Archives of Neurology and Psychiatry

VOLUME 41 FEBRUARY 1939 NUMBER 2

COPYRIGHT, 1939, BY THE AMERICAN MEDICAL ASSOCIATION

VARIATION IN VASCULARITY AND OXIDASE CONTENT IN DIFFERENT REGIONS OF THE BRAIN OF THE CAT

A. COLIN P. CAMPBELL, M.B., M.R.C.P. (EDINBURGH)
Rockefeller Traveling Fellow, 1935-1936
BOSTON

It has long been recognized that there is considerable variation in the amount of capillary bed available in different parts of the nervous system. However, only comparatively recently (following the example set by Krogh's work on the vascularity of muscle) has there been any attempt to measure this variation by accurate quantitative methods. Craigie investigated a large number of areas of the nervous system of the rat (1920,[1a] 1921,[1b] 1930 [1f]), of certain fish (1927,[1e] 1928 [1d]) and of birds (1929 [1e]). Cobb and Talbot [2] and Cobb [3] studied certain areas of the rabbit's brain, and Talbot, Wolff and Cobb [4] and Dunning and Wolff,[5] various parts of the nervous system of the cat.

The only extensive comparison of the vascularity of many areas was that of Craigie in the rat brain. It seemed profitable, therefore, to investigate a series of areas in the more highly developed brain of the cat, including the basal ganglia, cerebral neocortex, archicortex and cerebellar cortex.

From the Departments of Anatomy and Neuropathology, Harvard University Medical School, and the Department of Pathology, Edinburgh University.

1. Craigie, E. H.: (*a*) On the Relative Vascularity of Various Parts of the Central Nervous System of the Albino Rat, J. Comp. Neurol. **31**:429, 1920; (*b*) The Vascularity of the Cerebral Cortex of the Albino Rat, ibid. **33**:193, 1921; (*c*) Notes on the Vascular Supply in the Brain of a Holocephalian, Hydrolagus (Chimaera) Colliei, ibid. **43**:193, 1927; (*d*) The Vascularity of Various Parts of the Central Nervous System of the Dogfish, Squalus Sucklii (Girard), ibid. **46**: 97, 1928; (*e*) The Vascularity of the Cerebral Cortex in a Specimen of Apteryx, Anat. Rec. **43**:209, 1929; (*f*) The Vascular Supply of the Archicortex of the Rat: The Albino Rat, J. Comp. Neurol. **51**:1, 1930.

2. Cobb, S., and Talbot, J. H.: Studies in Cerebral Circulation: Quantitative Study of Cerebral Capillaries, Tr. A. Am. Physicians **42**:255, 1927.

3. Cobb, S.: Cerebral Circulation: Quantitative Study of the Capillaries in the Hippocampus, Arch. Surg. **18**:1200 (April) 1929.

4. Talbot, J. H.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: Changes in the Cerebral Capillary Bed Following Cervical Sympathectomy, Arch. Neurol. & Psychiat. **21**: 1102 (May) 1929.

5. Dunning, H. S., and Wolff, H. G.: The Relative Vascularity of Various Parts of the Central and Peripheral Nervous System of the Cat, and Its Relation to Function, J. Comp. Neurol. **67**:433, 1937.

The oxidase content of many of these areas was also studied, and the degree of correlation between this and the vascularity was examined, both these variable factors presumably being indexes of the metabolic activity of the various areas.

ESTIMATION OF VASCULARITY

METHOD

The brains of 5 cats were examined. Injections of a 50 per cent solution of india ink in distilled water were made. With the cat under dial anesthesia, the thorax was opened; a cannula was passed through an incision of the left ventricle into the aorta and tied in position; the descending aorta was clamped; the right auricle was opened to allow free venous return, and the injection was begun at a pressure of 120 mm. of mercury. After about 100 cc. had been perfused, the opening in the right auricle was clamped, and a further 50 cc. was injected at a pressure of 180 mm. of mercury, in order to distend the capillary bed as much as possible. The injection was thus synchronous with the death of the animal. The brain was removed and fixed in solution of formaldehyde U. S. P. (1:10); suitable blocks were then taken and embedded in pyroxylin. Sets of six serial sections (one of 200 microns and five of 20 microns) were cut, with intervals of 1 mm. between sets. The thick section made it possible to check the completeness of injection in each area examined. This was necessary, since the technic used by no means guaranteed a complete injection; the brains of several cats had to be discarded on this account. Furthermore, while the greater part of a brain might show reasonably complete injection, the thick sections sometimes revealed that in one or more areas the filling was incomplete; in these areas capillary measurements were therefore not made (hence the occasional blanks in the table and the portions made up of dotted lines in figure 1). Satisfactory injections were obtained in 5 cats.

The thin sections were stained with toluidine blue; the various regions could then be identified, while the staining was not sufficiently dark to obscure the capillaries filled with india ink. Fields of the desired regions were projected at a magnification of 600 on to paper ruled in areas of 6 by 12 cm. The choice of fields was haphazard, the only selection being the discarding of fields containing a large vessel. Such fields are not comparable with those containing capillaries only, since the larger intracerebral vessels are surrounded by a zone free from capillaries (Pfeifer[6]). For each area examined in each cat, three fields in each ten sections (two serial sets of five, with an interval of 1 mm.), or thirty fields, were thus projected. In the areas (lateral geniculate body, cerebral neocortex, archicortex and cerebellar cortex) within which several component laminae were examined separately, twenty fields were projected for each lamina. The portions of capillary within each field of 6 by 12 cm. were traced in pencil, and their lengths were later measured with a wheel map measurer, as suggested by Krogh[7] (appendix). When corrections for foreshortening were made, one obtained the total length of capillary in a unit of tissue of known area and thickness and could thus estimate the length of capillary, expressed in millimeters per cubic millimeter of tissue.

Corrections for foreshortening were made by noting the pieces of capillary which passed through the section from one surface to the other and calculating

6. Pfeifer, R. A.: Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

7. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1929, p. 375.

the error of foreshortening for each piece (the axis of its passage through the section being assumed to lie in one plane). When a piece of capillary dipped toward the center of the section (as shown by change in focus) and then returned to the same surface, it was assumed that the apex of the arc was at the center of the section, i. e., 10 microns from the surface, and the foreshortening was corrected individually for each area. As measurement of foreshortening of so many lengths of capillary proved extremely laborious, it was done for 1 animal (cat 2) only, and the coefficients thus obtained were used to correct the counts for the corresponding areas in the other cats. These coefficients varied in different areas from 1.069 to 1.188; i. e., correction for foreshortening made a difference of from + 7 to + 19 per cent in the count of capillary length.

It must be emphasized that the figures obtained are not absolute, for two reasons. First, no attempt was made to correct for the considerable degree of shrinkage that inevitably takes place during the process of dehydration and embedding, since one cannot assume that parenchyma and vascular mesh shrink to the same degree. Indeed, it is obvious that they do not with fixation in formaldehyde; the thick sections of the brains used showed a considerable degree of tortuosity of the vessels, which obviously was an artefact, since I have not seen it in later preparations of brains fixed in Susa's fixative after injection. Second, the correction for foreshortening, while better than no correction at all, leaves much to be desired. It is believed, however, that these fallacies do not seriously detract from the relative value of the estimations and that the method allows a reasonably accurate assessment of the relative vascularity of the different areas.

RESULTS

The results are summarized in the table and in the graphs (figs. 1 and 2).

Measurements of Vascularity, Expressed in Millimeters per Cubic Millimeter, of Various Regions of the Cat Brain

	Cat No.						
	1	2	3	4	5	Average	Index*
Globus pallidus	571	649	264	425	538	490	1.1
Putamen	885	1,058	586	725	689	790	1.8
Caudate nucleus	954	1,017	631	590	661	770	1.7
Thalamus							
Lateral	846	919	781	...	631	790	1.8
Dorsomedial	732	966	722	...	607	760	1.7
Ventral	1,074	1,049	844	630	752	870	2.0
Anterior	1,195	1,046	834	...	827	970	2.2
Lateral geniculate body							
Pars dorsalis B	.....	1,051	1,144	698	1,077	990	2.2
Pars dorsalis A_1	.....	1,441	1,185	1,115	1,190	1,230	2.8
Pars dorsalis A	.....	1,546	1,383	1,209	1,267	1,350	3.1
Parietal cortex							
Lamina I	974	1,075	720	880	673	860	2.0
Lamina II	949	1,233	823	872	796	930	2.1
Lamina III	1,200	1,239	963	1,089	819	1,060	2.4
Lamina IV	1,137	1,425	984	1,037	958	1,110	2.5
Lamina V	1,073	1,055	810	830	804	910	2.1
Lamina VI	1,088	1,032	754	779	721	870	2.0
Hippocampal region: dentate gyrus							
Lamina molecularis	737	909	710	...	633	750	1.7
Lamina granularis	543	665	501	...	448	540	1.2
Lamina multiformis	554	594	422	...	438	500	1.1
Hippocampus							
Lamina molecularis	892	905	706	...	628	780	1.8
Lamina radiata	459	582	363	...	366	440	1.0
Lamina pyramidalis	603	810	492	...	509	600	1.4
Lamina oriens	546	596	531	...	438	530	1.2
Cerebellar cortex							
Lamina molecularis	911	996	718	865	800	860	2.0
Lamina granularis	1,240	1,386	804	1,093	1,071	1,120	2.5

* In this column, the vascularity of each area is expressed as a multiple of that of the area (lamina radiata of the hippocampus) with the lowest vascularity of those examined.

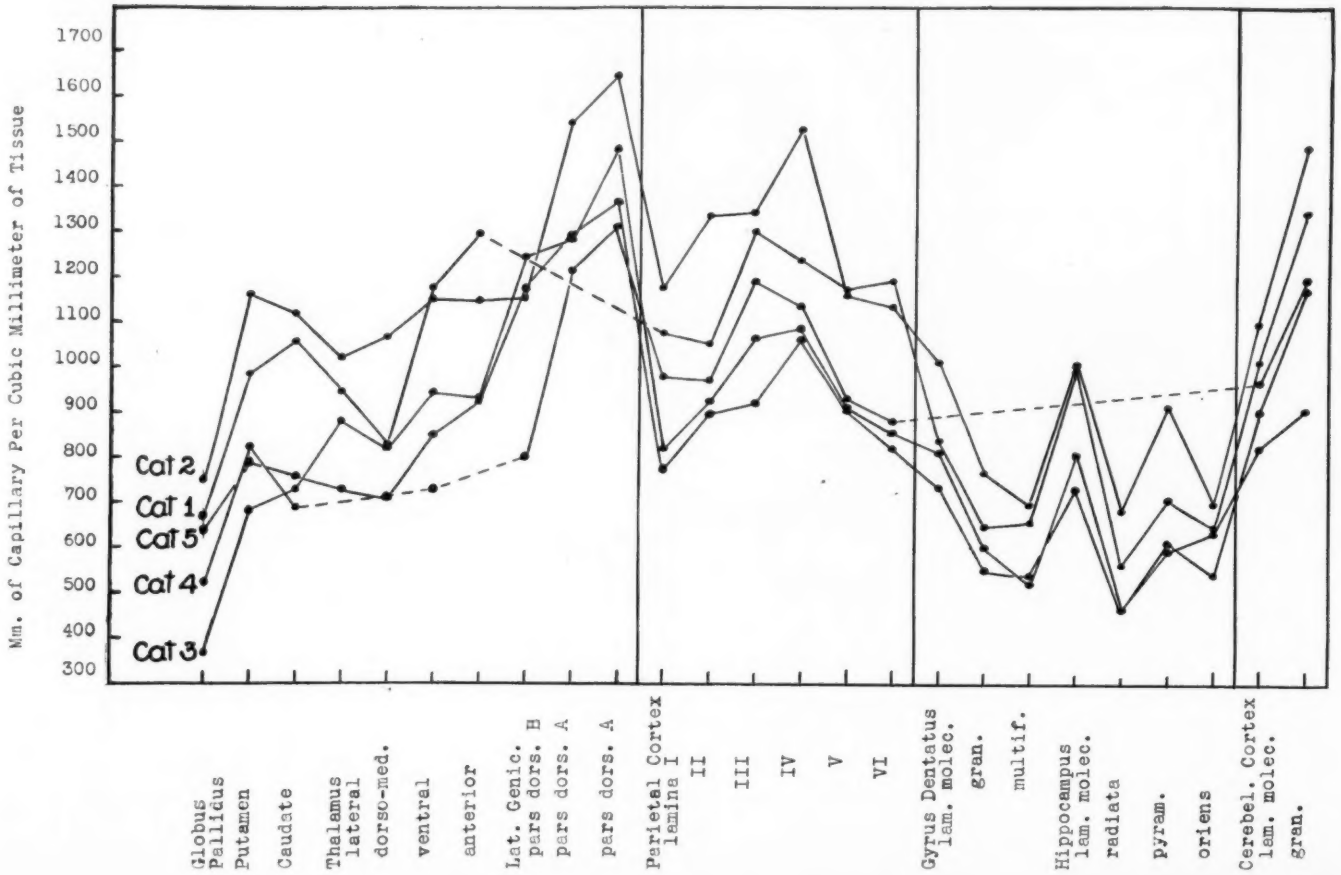

Fig. 1.—Curves showing the range of vascularity for each cat.

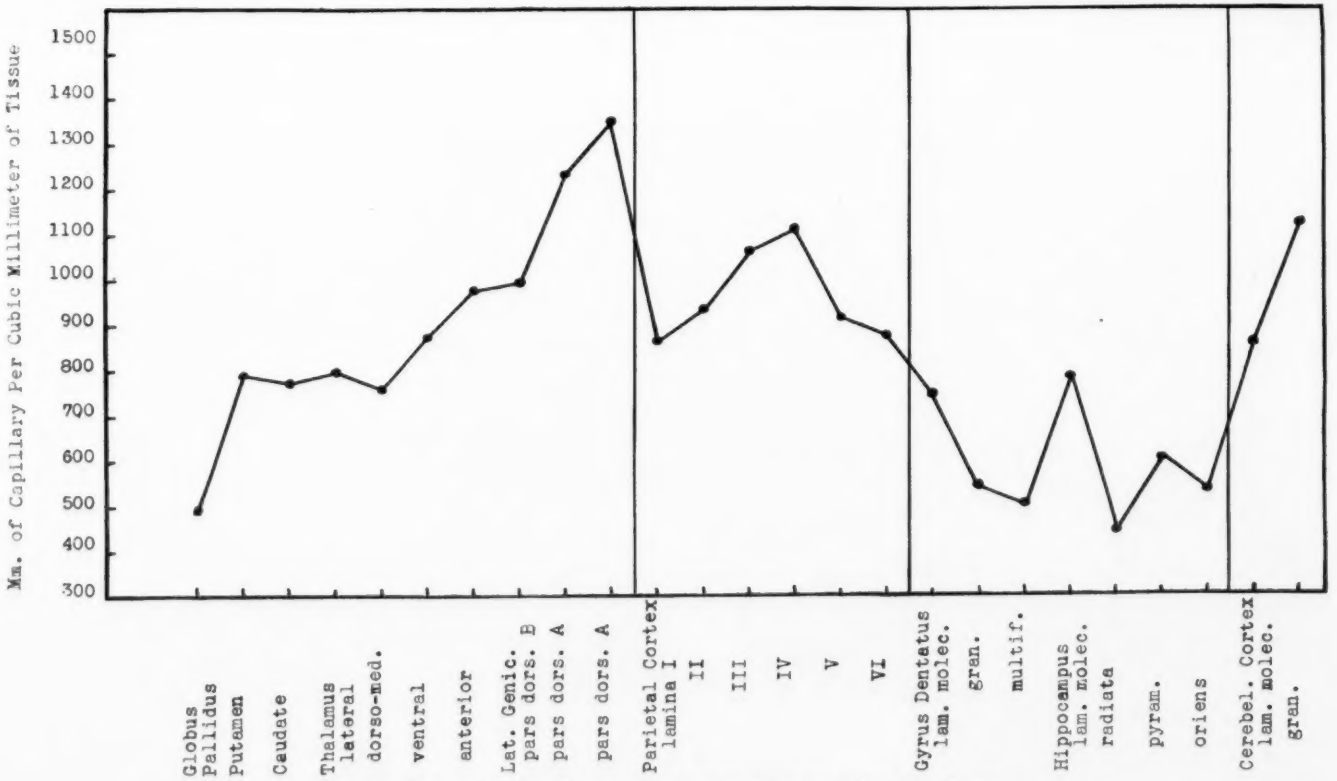

Fig. 2.—Curve showing the average range of vascularity for 5 cats.

COMMENT

It will be seen that, as Craigie observed in the rat, there are in the cat widely differing degrees of vascularity in the various areas of gray matter. They are most easily compared by expressing the results for each area as a multiple of the value for the least vascular area examined (the lamina radiata of the hippocampus) taken as unity.

Within the basal ganglia the variation is marked, ranging from the globus pallidus, with the low value of 1.1, to the lateral geniculate body, of which pars dorsalis (the most vascular area examined) has a value of 3.1. The strikingly low vascularity of the globus pallidus was well shown in thick sections (fig. 3), in which it was in sharp contrast to the

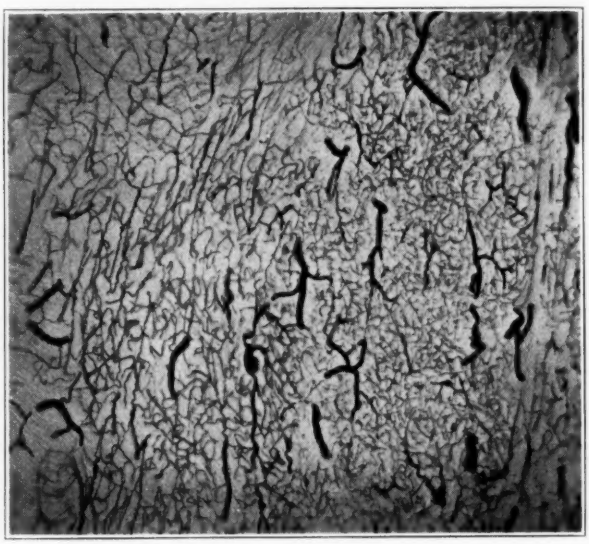

Fig. 3.—Section of the lenticular nucleus of the cat brain, 200 microns in thickness. India ink injection. The putamen appears on the right, the globus pallidus in the center and the white matter on the left. × 30.

much more vascular putamen (ratio 1.1 : 1.8) and was seen to be not much more vascular than the white matter. This contrast in vascularity between the globus pallidus and the putamen is evident also in the monkey (Macacus rhesus) and in man (fig. 4).

The caudate nucleus and the putamen are seen to be of approximately equal vascularity, as may be expected from their close functional relationship.

In investigating the nuclei of the thalamus, the limitations of the technic made it impossible to identify and consider separately the fine cytoarchitectural subdivisions; one was forced to confine oneself to a broad classification of the main nuclear masses and to make estimations

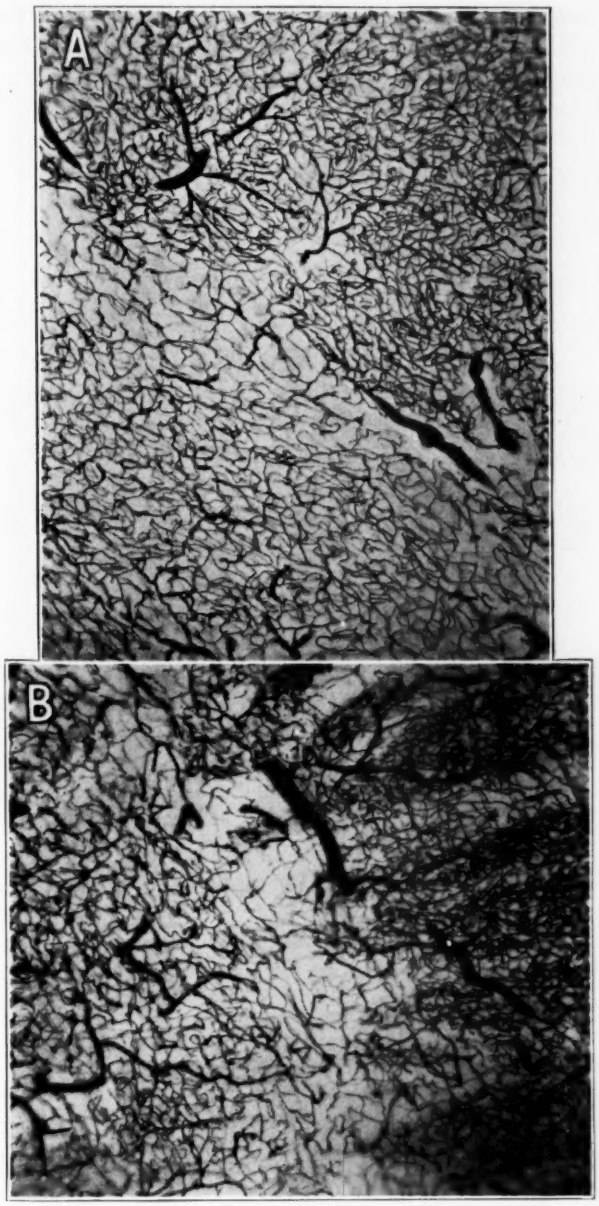

Fig. 4.—*A*, section of the lenticular nucleus of the monkey (Macacus rhesus), 200 microns in thickness. India ink injection. The putamen appears in the upper right and the globus pallidus in the lower left portion of the field. × 30. *B*, section of the lenticular nucleus of man, 200 microns in thickness. Pickworth peroxidase method. The putamen appears in the upper right and the globus pallidus in the lower left portion of the field. × 30.

of the vascularity of each of these as a whole. As the cell picture and, presumably, the functional activity may vary considerably within one of these main nuclear masses, it is of doubtful value to draw conclusions here concerning the correlation of function and vascularity. All one can say is that the range of vascularity in most of the nuclei of the cat's thalamus does not appear to be large (from 760 to 970 mm. of capillary per cubic millimeter of tissue, or, expressed as multiples of the vascularity of the hippocampal lamina radiata, from 1.7 to 2.2). The lateral geniculate body, however, stands out by reason of its extreme vascularity, the most vascular part having an index of 3.1, which surpasses any other parts of the brain that were examined.

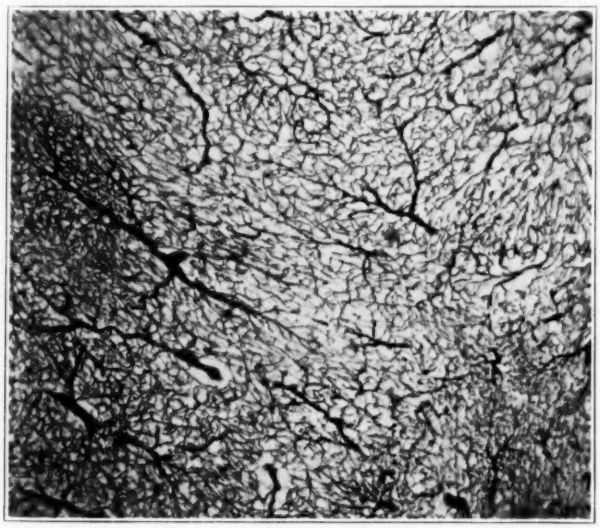

Fig. 5.—Section, 200 microns in thickness, of the thalamus of the monkey (Macacus rhesus). India ink injection. Above is the nucleus lateralis dorsalis, at the left the nucleus lateralis posterior and in the lower right corner the nucleus medialis dorsalis (pars dorsolateralis). The nuclei were identified according to Crouch's classification (J. Comp. Neurol. **59**:451, 1934). Note the great variation in vascularity. × 30.

The comparative uniformity of vascularity in the thalamus of the cat does not appear to be reproduced in the thalamus of the monkey. No actual measurements have been made in the monkey, but examination of thick sections of monkey brains in which injections were made indicates a much wider degree of variation, corresponding, no doubt, to a higher degree of functional differentiation (fig. 5).

In the hippocampal region the striking feature is the general low degree of vascularity. The vascularity of the molecular layers of the dentate gyrus and the hippocampus (1.7 and 1.8, respectively) approxi-

mates the general level of vascularity of the basal ganglia and the less vascular neocortical layers; the other laminae of the archicortex fall far below the general level of the gray matter of the brain (table and figs. 1 and 2). The values given here for the cat correspond remarkably closely, both relatively and absolutely, with Craigie's [1f] figures for the corresponding laminae of the archicortex of the albino rat. Cobb's [3] figures for the archicortex of the rabbit showed a similar range and order of vascularity in the comparable areas which he examined.

The six laminae of the neocortex (parietal region, gyrus suprasylvius medius) show a variation from 2 to 2.5 (860 to 1,110 mm. per cubic millimeter). The observations here with regard to the relative vascularity of the various layers agree reasonably closely with those of Craigie in the neocortex of the rat, although the figures for the parietal cortex of the rat were all a little higher. The present observations agree also with those of Dunning and Wolff [5] for the parietal cortex of the cat, although their figures were considerably lower; this is explained in part by the fact that these authors appear not to have allowed for foreshortening and in part, perhaps, by choice of a different region of the parietal cortex. It is apparent that in the cat, as in the rat, lamina IV of Brodmann is the most vascular area, with lamina III a close second. Lorente de Nó [8] reported the same observation (though without making counts) in the monkey and rabbit.

In the cerebellar cortex the range of vascularity (from 2 to 2.5 in the molecular and granular layers, respectively) is similar to that in the parietal neocortex. The absolute values are similar to those found by Craigie [1a] for the rat's cerebellar cortex; the figures were slightly higher in the case of the rat, but probably not significantly so in view of the difference in technic. The ratio of vascularity of the two layers in the rat was almost identical with that found in the cat.

VARIATION IN THE OXIDASE CONTENT OF DIFFERENT REGIONS OF THE BRAIN

The oxidase activity of brain tissue, as demonstrated by the indophenol reaction, was investigated in 1912 by Pighini.[9] He showed that the gray matter gives a positive oxidase reaction, while the white matter does not. Katsanuma [10] made a wider investigation of the incidence of the indophenol-oxidase reaction, demonstrating positively reacting granules in the cerebral and cerebellar cortex and in the basal ganglia. How-

8. Lorente de Nó, R.: Ein Beitrag zur Kenntnis der Gefässverteilung in der Hirnrinde, J. f. Psychol. u. Neurol. **35**:19, 1927.

9. Pighini, G.: Ueber die Indophenoloxydase im Zentralnervensystem, in der Tela chorioidea und in der Cerebrospinalflüssigkeit, Biochem. Ztschr. **42**:124, 1912.

10. Katsanuma, S.: Zur Frage der Naphtholblauoxydasereaktion des Nervensystems, Beitr. z. path. Anat. u. z. allg. Path. **60**:150, 1915.

ever, credit is due Marinesco [11] for the most complete survey of the incidence of the reaction in the central and peripheral nervous systems. He showed that gray matter everywhere gives a positive reaction; blue-staining granules (indicating the synthesis of indophenol, under the influence of oxidase) were seen in the cytoplasm, but not in the nucleus, of all ganglion cells; the reaction was positive in the dendrites but not in the myelinated axons, hence the negative reaction of white matter. Aside from obviously intracellular oxidase, the gray matter between the ganglion cells was diffusely studded with fine blue granules; these, he suggested, were associated with the fine synaptic fibers of the cell processes. Ganglion cells of the cranial nerve ganglia, posterior root ganglia and sympathetic ganglia gave a positive reaction. So did certain nerve end organs (Meissner's corpuscles and pacinian bodies). Glia cells showed no oxidase reaction.

As Marinesco pointed out, the oxidase that is demonstrated by the indophenol reaction is probably not the only means by which the nerve tissue is enabled to utilize oxygen. The white matter, which has been shown by Holmes [12] and others to have a definite, if relatively low, oxygen consumption, gives a negative oxidase reaction. The universal distribution of the indophenol-oxidase reaction in gray matter, however, suggests that in this tissue it is an essential part of the mechanism of metabolism, and one would expect it, therefore, to vary in quantity in different regions in proportion to the varying oxygen consumption of those regions. For this reason, it seems profitable to assess its quantitative incidence in the regions of the cat's brain, the vascularity of which has been measured, and to see to what extent this incidence confirms the degree of vascularity as an index of metabolic activity.

MATERIAL AND METHOD

Various parts of the nervous system were examined in 5 cats. The animals were lightly anesthetized with dial (intraperitoneally) or ether and killed by intravenous injection of air. The brains were removed and blocks taken as quickly as possible. Thereafter the procedure was essentially that employed by Marinesco and Katsanuma. Frozen sections were cut from fresh, unfixed tissue and placed directly from the knife into the reagent. (It was not possible to obtain good sections of less than 50 microns in thickness.) The reagent was made up according to Graf's method, i. e., equal parts of a 0.05 per cent solution of alphanaphthol and of dimethylparaphenylenediamine in a physiologic solution

11. Marinesco, G.: Recherches histologiques sur les oxydases, Compt. rend. Soc. de biol. **82**:98, 1919; Études histologiques sur les oxydases, et les peroxydases, ibid. **82**:258, 1919; Récherches histo-chemiques sur la rôle des ferments oxydants dans les phénomènes de la vie à l'état normal et pathologique, Ann. d'anat. path. **1**:121, 1924.

12. Holmes, E. G.: Oxidations in Central and Peripheral Nervous Tissue, Biochem. J. **24**:914, 1930.

of sodium chloride, freshly prepared, were filtered and mixed immediately before use. After a few minutes in this mixture, the gray matter of the sections acquired a violet-blue tinge, indicating a positive oxidase reaction.

The sections were left for at least fifteen minutes in the mixture by which time the reaction had reached its maximum. They were then placed on slides without washing, allowed almost to dry and mounted in Farrant's medium.

These preparations must be examined at once; the reaction begins to fade within a few hours. While the color of the reaction may be made permanent by passing the sections through solutions of iodine and lithium carbonate, it loses a great deal of its vividness thereby.

RESULTS

Certain fallacies must be borne in mind in interpreting the results. The indophenol-oxidase reaction in nerve tissue is extremely labile (hence the need of using fresh, unfixed tissue and of avoiding any washing of the sections), so that in any one animal the comparison of areas in different blocks is unreliable, since the blocks have inevitably been exposed for slightly different periods to room temperature. This fallacy may be minimized by keeping the blocks surrounded by ice while awaiting their turn for sectioning. In practice, however, it was found that the strength of the reaction varied in sections from different blocks and in different sections from the same block. In assessing the relative oxidase content of different regions, therefore, the most satisfactory comparisons are those made between different regions in the same section. However, when gross and constant differences are seen in several brains between regions comparable only in different sections, it appears permissible to make a quantitative comparison, provided that a further fallacy is guarded against, i. e., variation in the thickness of sections. With the technic employed it is extremely difficult to cut sections of a constant thickness. Before comparisons of the strength of the oxidase reaction of different areas are made, therefore, it is necessary to be sure, by careful focusing of the microscope, that the vertical depth of the section is approximately the same in the regions compared.

In the lenticular nucleus the difference in oxidase reaction between the globus pallidus and the putamen was marked; the large ganglion cells of the globus pallidus contained a rich content of oxidase-positive granules in their cell bodies and dendrites (fig. 6); the intercellular gray matter, however, was relatively poor in positive granules, so that the general concentration of positive granules was low as compared with that in the putamen (fig. 7), where the intercellular tissue as well as the cell bodies was rich in oxidase. The correlation with the relative vascularity of the two regions is obvious.

As for the rest of the basal ganglia, the thalamus showed an oxidase picture similar to that of the putamen. No detailed comparison of different nuclei within the thalamus was possible, but no gross local

Fig. 6.—Globus pallidus of the cat. Indophenol-oxidase reaction; × 300.

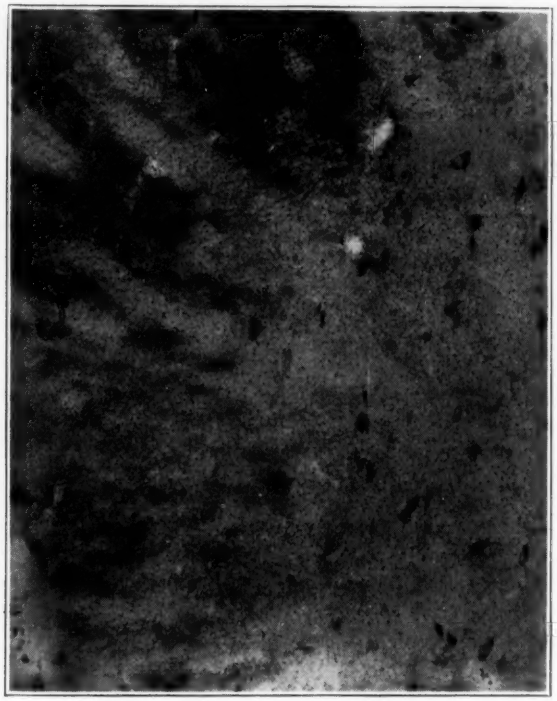

Fig. 7.—Lenticular nucleus of the cat. Indophenol-oxidase reaction. In the upper right portion is the putamen, and in the lower left corner, the globus pallidus. In the latter note the scattered, strongly oxidase-positive ganglion cells and the comparative poverty in oxidase of the tissue as a whole, as compared with the putamen. × 60.

differences were noted. (Unfortunately, satisfactory sections including the lateral geniculate body were not obtained.)

The oxidase content of the parietal neocortex was examined in approximately the same area (gyrus suprasylvius medius) as that in which the estimations of vascularity had been made. Figure 8 shows that the supragranular layers have a much richer oxidase content than the infragranular layers. Lamina IV appears to be the richest, and lamina V the poorest; individual large pyramidal cells in this layer can be seen in the photomicrograph to stand out with a strong oxidase reaction, but the intercellular tissue is relatively poor in positive granules. It should be mentioned, as Marinesco pointed out, that the ganglion cell

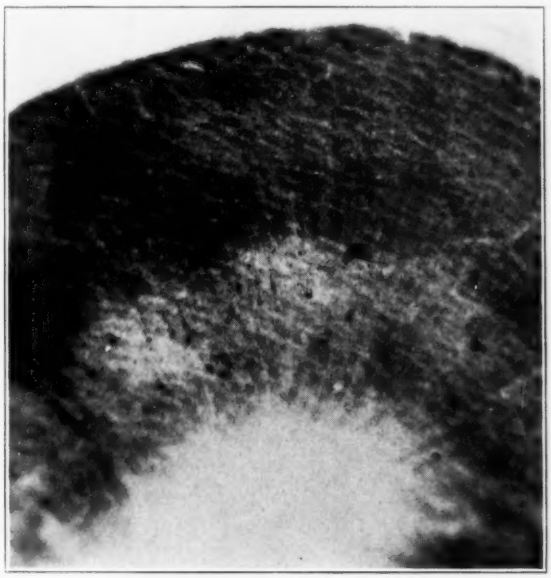

Fig. 8.—Parietal neocortex (gyrus suprasylvius medius) of the cat. Indophenol-oxidase reaction. Note the rich oxidase content of layers I to IV and the comparative poverty of layers V and VI. × 40.

bodies do not all give an equally strong reaction; strongly reacting cells in all areas were seen side by side with poorly reacting or negative cells. In a photograph such as figure 8, therefore, all the ganglion cells present are not visible.

Bielschowsky and Rose (1927) observed a similar distribution of oxidase in the motor and sensory cortex of dogs and monkeys; they stated that laminae III and IV give the strongest reaction. They differed, however, in obtaining a weak reaction in lamina I, whereas in the present study lamina I constantly gave a strong reaction.

The correlation between oxidase content and vascularity in this part of the neocortex was suggestive, but not exact. Lamina IV showed good correlation, as did the infragranular layers. But laminae I and II had an oxidase content richer than their vascularity would suggest. There is, however, a possible explanation of this discrepancy. The degree of capillary vascularity is presumably an index of the relative rate of metabolic activity in comparable areas when the rate of flow in the capillaries is the same. If there were reason to believe that the rate of flow is greater in the capillaries of the two most superficial layers than in those of the deeper layers, one could explain the discrepancy between capillary bed and oxidase content in the former. There is available no evidence of such a difference in rate of flow, but there is indication of a local difference in the type of supplying arterioles. It has been stated that in man (Freedom [13]) and in the cat (Campbell [14]) there is a tendency for the superficial and the deep cortical laminae, respectively, to receive their blood from arterioles of different types. For instance, in the cat the superficial layers are supplied mainly by short arterioles, ending in the capillary mesh soon after their entrance from the pia, while the deeper layers are supplied by longer arteries, which in many cases give off no branches to the superficial layers as they pass through them. Admittedly, as Pfeifer [6] has shown, all these arterioles open into a capillary mesh which is continuous. If, however, the superficial and the deep parts of the mesh are fed by arterioles of different types (though not, of course, exclusively), it is reasonable to believe that the rate of flow may differ in these two parts of the mesh and may be faster in the part which is fed more directly from the superficial vessels.

It is not desired to emphasize this hypothetic factor of variation in the rate of capillary flow. It is a point, however, which cannot be entirely disregarded in assessing the rate of metabolic activity from the degree of capillary vascularity.

In the hippocampal region assessments of oxidase content were difficult, owing to the trouble in securing sections of even thickness. In the gyrus dentatus, however, it was clear that the correlation between oxidase content and vascularity was close. Figure 9 shows that the molecular layer (on the left) gives the strongest oxidase reaction, the granular and multiform layers being much weaker. The granular layer shows the nuclei of the closely packed ganglion cells as clear round spaces, surrounded by narrow rings of fine blue granules, most of which appear to be in the cytoplasm of the cell bodies; the cells are so closely packed that there is little room for intercellular granules. If Marinesco

13. Freedom, cited by Jakob, A.: Normale und pathologische Anatomie und Histologie des Grosshirns, Leipzig, Franz Deuticke, 1929, vol. 2, pt. 1, p. 487.

14. Campbell, A. C. P.: The Vascular Architecture of the Cat's Brain: A Study by Vital Injection, A. Research Nerv. & Ment. Dis., Proc. **18**:69, 1938.

is correct in his suggestion that the intercellular granules are related to fine synaptic fibers, this picture suggests that synapses are not numerous in the granular layer of the gyrus dentatus.

In the hippocampus itself the lamina radiata (the least vascular layer) was consistently poor in oxidase. No consistent difference could be determined in the other layers.

In the cerebellum both the molecular and the granular layers gave a strong oxidase reaction (fig. 10). The distribution was much more uniform in the molecular layer. The flocculated appearance of the reaction in the granular layer corresponded to the grouping of the

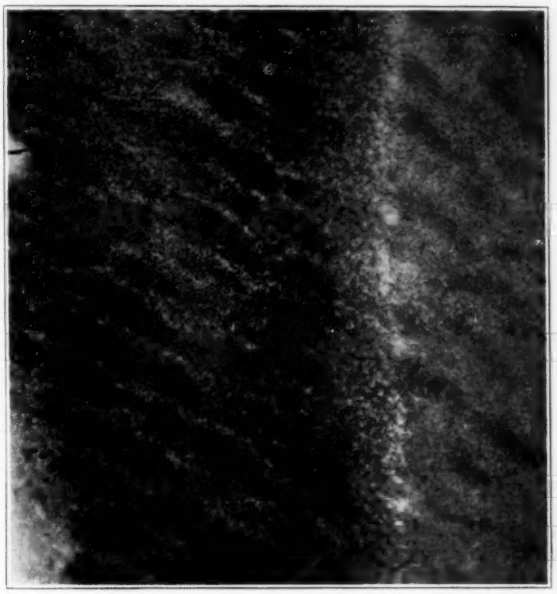

Fig. 9.—Archicortex (gyrus dentatus) of the cat. Indophenol-oxidase reaction. At the left, is the oxidase-rich molecular layer; at the right, the polymorphic layer, and a little to the right of center, the granular layer (both of which are relatively poor in oxidase). × 120.

granule cells; in the more open areas the oxidase reaction was strong. It appears, therefore, that a large amount of the oxidase in this layer was intercellular. The bodies of the Purkinje cells contained many oxidase-positive granules, and these could be traced also along the dendrites in the molecular layer with great clarity, as the photomicrograph shows.

The flocculated distribution of oxidase in the granular layer made it difficult to compare the two layers quantitatively; also, it proved hard to obtain sections of uniform thickness, the parts occupied by the molec-

ular layer tending to be thinner and producing therefore a fallacious lowering of the apparent strength of the reaction in that layer. This fallacy is present to some extent in the field illustrated in figure 10. On the whole, however, when areas of uniform thickness could be found for comparison, the reaction appeared to be stronger in the granular layer and showed therefore a positive correlation with the relative vascularity of the two layers. This does not agree with the results of Bielschowsky and Rose,[15] who stated that in the dog and monkey the granular layer gives a definitely weaker reaction than the molecular layer.

It is interesting to contrast the granular layer of the cerebellum with that of the gyrus dentatus (figs. 9 and 10); both consist of small,

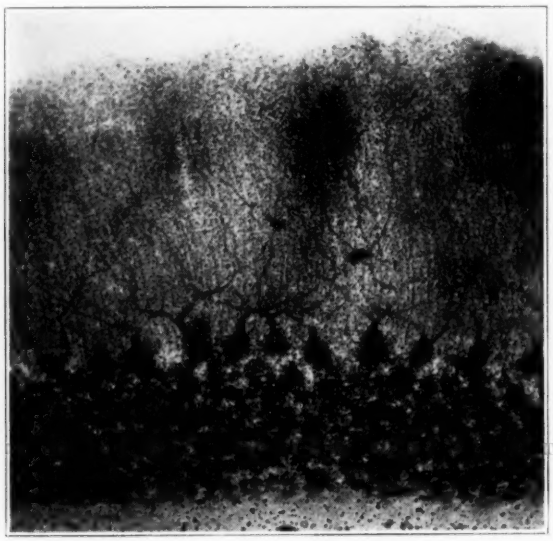

Fig. 10.—Cerebellar cortex of the cat. Indophenol-oxidase reaction. Above is the molecular layer; below, the granular layer. × 120.

densely packed cells. Their oxidase content and their vascularity were vastly different, however, the granular layer of the cerebellum having the greater value for both.

In the present study no investigations were made of the vascularity of sensory or sympathetic ganglia. In view, however, of the recent work on this subject by Dunning and Wolff,[5] the oxidase contents of these two types of ganglia were compared. Figure 11 shows a typical field from the trigeminal ganglion, and figure 12, a field from the superior

15. Bielschowsky, M., and Rose, M.: Die Bedeutung des Nachweises oxydierender und reduzierender Gewebsfermente für Lokalisationsfragen des Gehirns, J. f. Psychol. u. Neurol. **33**:73, 1927.

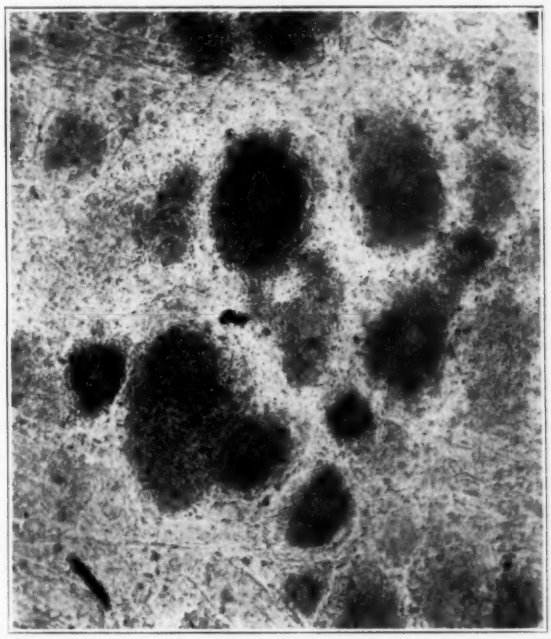

Fig. 11.—Trigeminal ganglion of the cat. Indophenol-oxidase reaction. × 300.

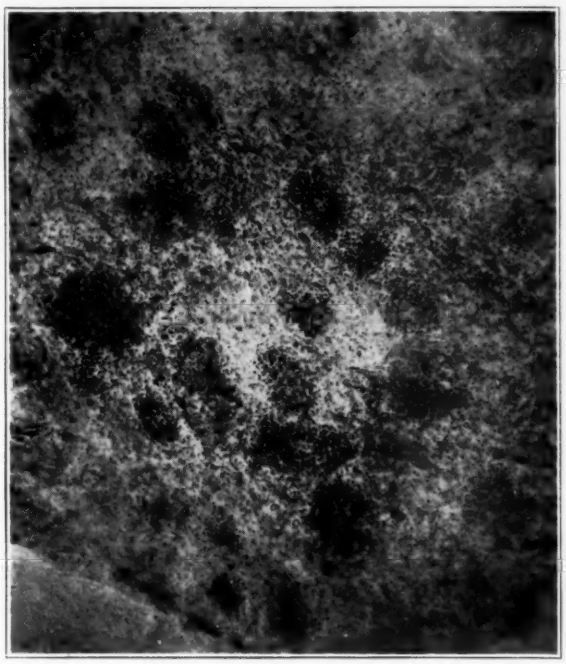

Fig. 12.—Superior cervical sympathetic ganglion of the cat. Indophenol-oxidase reaction; × 300.

cervical sympathetic ganglion. The ganglion cells of both are well supplied with oxidase-positive granules. At first sight, the cells of the trigeminal ganglion appear richer, but this is probably due to the larger size of the cells, their greater depth producing an apparently darker reaction. The intercellular tissue, however, shows a marked difference in the two ganglia, being studded with positive granules in the sympathetic ganglion and giving a negative reaction in the trigeminal ganglion, as well as in the posterior root ganglia. This difference is due, no doubt, to the presence of dendrites and synapses in the sympathetic and their absence in the trigeminal ganglion. The total concentration of oxidase appears to be greater in the former, giving therefore a positive correlation with the degree of vascularity as shown by Dunning and Wolff. The figures of these authors showed a ratio of vascularity of 1.4:1 for the sympathetic and the sensory ganglia, respectively. Further, it should be noted that the concentration of oxidase within the cell bodies is not lower in the sensory than in the sympathetic ganglia; there is no reason to suppose, therefore, that the difference in vascularity, and presumably in the rate of oxygen consumption, depends on an inherently different rate of respiration of the cytoplasm in the two types of ganglia. The difference appears to be dependent purely on the absence of dendrites and synapses in the one and their presence in the other.

GENERAL COMMENT

A general survey of the range of vascularity in the areas examined indicates a certain correlation between vascularity and content of ganglion cells. Thus, within the basal ganglia, the globus pallidus, the corpus striatum and the lateral geniculate body, in the order of cellularity, fall into the same order with regard to vascularity. In the parietal neocortex lamina IV is at once the most cellular and the most vascular. In the cerebellar cortex, also, the cellular granular layer is more vascular than the molecular layer. However, as Lorente de Nó,[8] Pfeifer [16] and Dunning and Wolff [5] have pointed out, there are exceptions to this rule. The present investigation confirms this. For instance, in the parietal cortex layers I and VI have an approximately equal vascularity but a different cellularity. In the cerebellar cortex, though the molecular layer is less vascular than the granular, the difference is much less marked than the difference in cellularity. The gyrus dentatus furnishes an extreme example. The excessively cellular granular layer is almost 50 per cent less vascular than the poorly cellular molecular layer.

16. Pfeifer, R. A.: Grundlegende Untersuchungen für die Angioarchitektonik des menschlichen Gehirns, Berlin, Julius Springer, 1930; Diskrepanzen zwischen der Cytoarchitektonik und Angioarchitektonik des menschlichen Gehirns, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1933, p. 247.

Dunning and Wolff [5] recently estimated the mass of cytoplasm of ganglion cell bodies in the trigeminal ganglion, the superior cervical sympathetic ganglion and the parietal cortex of the cat and showed that, while the cytoplasmic mass is greatest in the trigeminal ganglion and least in the parietal cortex, the relative vascularity is the reverse. They make the attractive suggestion that vascularity is proportional to surface area of neural cytoplasm and that vascularity is therefore especially rich in areas where the cytoplasm is finely divided in many synaptic processes, such processes producing a relatively high total surface area as compared with the mass of cytoplasm. The excess in degree of vascularity, therefore, over that to be expected from the demonstrable cytoplasmic mass of a region should be an index of the richness of that region in synaptic processes.

A possible objection to this conclusion is that a region with many synapses and a relatively high rate of oxygen consumption may have a relatively low vascularity which is compensated for by a rapid rate of blood flow through the capillary bed. The oxidase content, however, may be expected to be proportionate to the oxygen consumption rather than to the anatomic degree of capillary vascularity, and should therefore be a check on the possible intervention of the factor of rate of capillary flow. If the correlation between oxidase content and capillary vascularity is positive, it is unlikely that the varying rate of flow is a factor, and the assumption that the degree of vascularity is a reliable index of the rate of metabolism is strengthened. This correlation is, in general, positive, as can be seen from the results already cited, the only obvious exceptions being laminae I and II of the parietal neocortex, in which the factor of a different rate of blood flow is tentatively suggested.

The histologic demonstration of the total content of synapses of a region is difficult. Two indexes of the richness in synapses have been suggested: first, excess of vascularity over that expected from the cytoplasmic mass (Dunning and Wolff) and, second, richness of the region in finely distributed intercellular oxidase-positive granules (Marinesco). Neither of these indexes can be regarded as unequivocably established. Each, however, is strengthened by the present demonstration of the generally positive correlation between them in the regions examined.

SUMMARY

The vascularity of a series of regions in the cat's brain, including the basal ganglia, parietal neocortex, archicortex and cerebellar cortex, has been measured.

The archicortex generally is of low vascularity; the least vascular area of all those examined is the lamina radiata of the hippocampus.

In the basal ganglia the globus pallidus is of very low vascularity; the lateral geniculate body is the most highly vascular area of those examined.

In the parietal neocortex laminae III and IV are the most vascular; the other laminae are of approximately equal vascularity.

The cerebellar cortex has a range of vascularity approximately the same as that of the parietal neocortex, the granular layer being the more vascular.

The oxidase content of many of these areas has been examined. In general, it shows a positive correlation with the degree of vascularity. The position of both, therefore, as indexes of local metabolic activity is strengthened. It is tentatively suggested that a negative correlation may be explained by local variations in the rate of blood flow in the capillary bed.

Prof. Stanley Cobb and Prof. George B. Wislocki advised me in this study.

STUDIES IN MONGOLISM

II. THE THYROID GLAND

CLEMENS E. BENDA, M.D.
WRENTHAM, MASS.

In a previous paper,[1] it was demonstrated that the mongoloid appearance is due to a prenatal disturbance affecting the formation of the skull. The small stature of the mongoloid patient is due to lack of proliferation of the cartilage and early closure of the epiphysial lines, so that the growth of the bones is early arrested. It was proved that mongolism is neither a racial mutation nor an atavistic regression.

The previous observations were presented to facilitate understanding of the pathologic changes in the endocrine glands associated with this condition. My chief interest in the present investigation was centered in the thyroid, known as one of the most important glands in relation to growth and differentiation of the organism.

The adrenal glands have recently been studied by Hirning and Farber;[2] therefore I shall not discuss this material in detail. My observations in 3 new cases of mongolism coincide with those made by Hirning and Farber. It may be sufficient, therefore, to repeat their conclusions concerning the adrenal glands.

1. The width of the permanent cortex of mongols in the first year of life does not differ essentially from that of controls of the same age.

2. There is a definite lack in the growth of the permanent cortex in the older mongols, as compared with the control group.

These observations are of interest in view of the fact that authors have recently called attention to changes in the adrenals. Their conclusions were not supported by pathologic studies, and I cannot believe that the adrenals play an important role in mongolism.

From the Research Department for the Study of Mental Deficiency, Wrentham State School, and the Department of Neuropathology, the Harvard University Medical School, Boston.

1. Benda, C. E.: Studies in Mongolism: I. Growth and Physical Development, Arch. Neurol. & Psychiat. **41**:83 (Jan.) 1939.

2. There is a definite lack in the growth of the permanent cortex in the older in Mongolism, Am. J. Path. **10**:435 (May) 1934.

MATERIAL

Material from autopsies in 21 cases [3] was available for my pathologic studies, but in some instances microscopic examinations were not completed. Sections of the thyroid in 14 cases were studied, in order to draw conclusions with regard to the structure of this gland in mongolism.

Drs. Tracy B. Mallory and Charles S. Kubik gave me opportunity to study the material in a case from the Massachusetts General Hospital. The material in 18 cases was obtained from the Children's Hospital, Boston. Dr. Sidney Farber permitted me to use this material.

In the microscopic study, it was obvious that the amount of pathologic change varied in different sections of the same gland. The more material that was available in a case the more strikingly apparent were the pathologic changes. Therefore, I cut as many sections as possible; in some older cases from the Children's Hospital only one slide was available for study. Even this section was sufficient, however, to show changes similar to those noted in the other cases.

The material was fixed in Zenker's fluid or solution of formaldehyde, embedded in paraffin and stained with eosin or phloxine and methylthionine chloride (methylene blue), alum-hematoxylin and eosin or the Mallory tricolor stain.

PROTOCOLS

CASE 1.—*Mongoloid girl aged 9 days* (3 slides).

On both sides of the trachea two small lobes of the thyroid were visible. At the periphery of the lobes the acini were mostly enlarged to a diameter of from about 130 to 200 microns. They were folded and irregular in shape, and confluence of different vesicles was noticeable. The acini contained bright, pinkish-stained, rather thin colloid. Some colloid was visible between the vesicles. The acini were walled with epithelial cells with large round nuclei. The nuclei were mostly transparent, with a fine granular structure. They varied in shape and staining reactions. Between the acini were increase in connective tissue and piles of epithelial cells without formation of acini.

The central part of the gland consisted chiefly of dense tissue composed of thickly piled epithelial cells and connective tissue. There were many red blood cells within the tissue. There was little formation of acini, and these were small and irregular and did not contain colloid.

CASE 2.—*Mongoloid girl aged 6 weeks* (9 slides).

The thyroid weighed 1 Gm. At the periphery follicles were enlarged up to 200 microns and contained faintly stained colloid. The outline of these vesicles was irregular. The epithelial cells of the walls of the vesicles had deeply blue-stained nuclei without visible chromatin structure. The vesicles in the other parts of the gland did not contain colloid. They were small, irregular and walled with deep, dark, nucleated cells. Besides the vesicles, there were large piles of epithelial cells without formation of acini. The cells were small and dark and lay in thick strips of connective tissue. The entire gland was hypoplastic and of so-called fetal structure.

CASE 3.—*Mongoloid boy aged 2 months.*

The acini were irregular in shape. Some were enlarged and folded. They contained colloid, which stained deep red and was retracted from the walls. The

3. In 2 cases (cases 7 and 9) autopsies were performed at the Wrentham State School.

walls of the enlarged, unfolded vesicles consisted of cylindric epithelium. The other sections of the gland showed an irregular increase of parenchyma cells and connective tissue (fig. 1).

CASE 4.—*Mongoloid boy aged 2½ months.*

Only a small amount of glandular tissue of the thyroid was seen, lying between connective tissue on well developed musculature around the cartilage of the trachea. This glandular tissue showed only a few real acini, which were enlarged and walled with flat epithelium. The other parts consisted of irregular-growing parenchyma with deeply blue-stained nuclei. This tissue was of embryonic type. No real colloid was present in the vesicles.

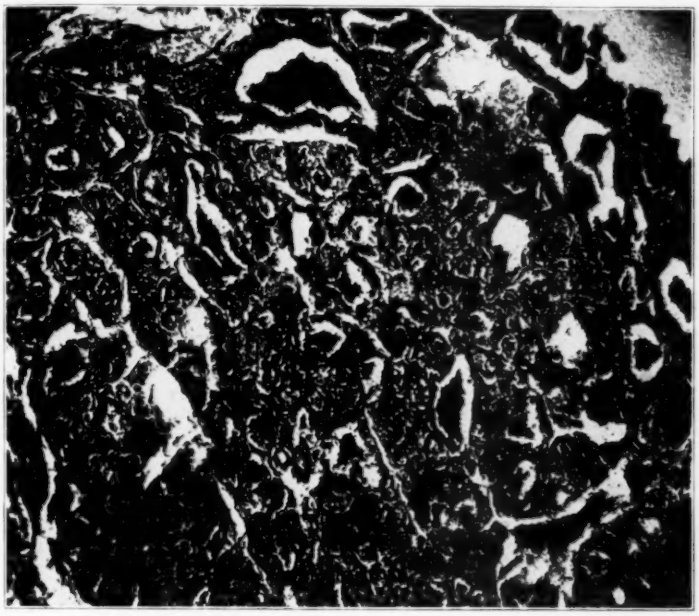

Fig. 1.—Section of the thyroid gland of a 2 month old mongoloid child. The irregular acini contain colloid, which is retracted from the walls. The greater part of the picture shows irregular growth of parenchymal cells, forming small irregular acini without any production of colloid.

CASE 5.—*Mongoloid boy aged 3 months* (8 slides).

The thyroid showed irregular acini of various sizes, filled with red-stained colloid. The nuclei of the epithelial cells were large and irregular in shape. The epithelial layer was sometimes duplicated, and there was an irregular growth of epithelial cells between the acini without formation of vesicles. In some parts the connective tissue was much increased.

CASE 6.—*Mongoloid boy aged 4½ months* (6 slides).

The thyroid contained many enlarged acini, which were irregular in shape and folded, and the epithelial layer seemed in some places to be duplicated. The size of such acini was about 400 microns. One measured more than 600 microns. In

some parts the epithelial wall was destroyed, and the colloid lay about the acini. Within such areas of colloid degeneration could be seen portions of the original wall of the tubules. In other parts the irregular acini did not contain colloid, and the walls of the vesicles were sometimes duplicated. Between such areas of preserved glandular tissue were many piles of epithelial cells without regular tubular structure. Connective tissue was increased.

CASE 7.—*Mongoloid child aged 5 months* (20 slides).

At autopsy the thymus and thyroid were observed to be closely associated. It was not possible to separate them properly in the gross specimen. It was obvious that the thyroid was small and had undergone cystic degeneration, whereas the thymus was hypertrophic.

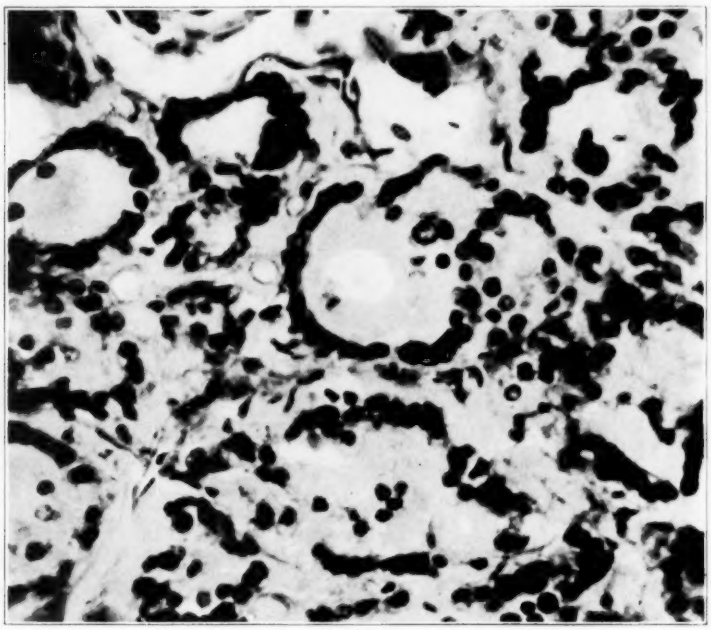

Fig. 2.—Section of the thyroid of a 5 month old mongoloid child. The walls of the vesicles are irregular and are destroyed in some parts. The nuclei of the cells are irregular and stain dark, without fine chromatin structure. The acini contain colloid. Much free colloid was observed between the walls within the spaces.

The small glandular nodules which were seen between areas of overgrowth of connective tissue showed enlarged acini filled with colloid, which stained red or pinkish and was mostly retracted from the walls. In many parts there were no vesicles at all. The walls of the acini were of cylindric epithelium and showed large nuclei, which stained alternatingly deep blue and red. The preserved acini were irregular. Around the acini was an overgrowth of epithelial cells. In other sections of the gland there was abundant proliferation of irregular epithelial cells which did not form glandular structures. Large sections of the glandular tissue showed colloid degeneration of the entire tissue. The colloid filled all spaces between the acini, and many walls were destroyed, so that the epithelial cells were floating within the colloid (fig. 2).

CASE 8.—*Mongoloid child aged 6 months* (7 slides).

The histologic picture varied remarkably in different sections. Only the study of many slides gave a justifiable impression of the pathologic changes. Many acini were enlarged to 200 or 300 microns. They were folded, and prominent papillae protruded into the lumen. There was confluence of many follicles, which contained colloid. In some sections this colloid stained a bright pink and was mostly retracted from the walls. In other sections the colloid stained darker blue and seemed to be more solid. The epithelial walls were irregular and sometimes duplicated. Many smaller tubules were irregular in form and did not contain

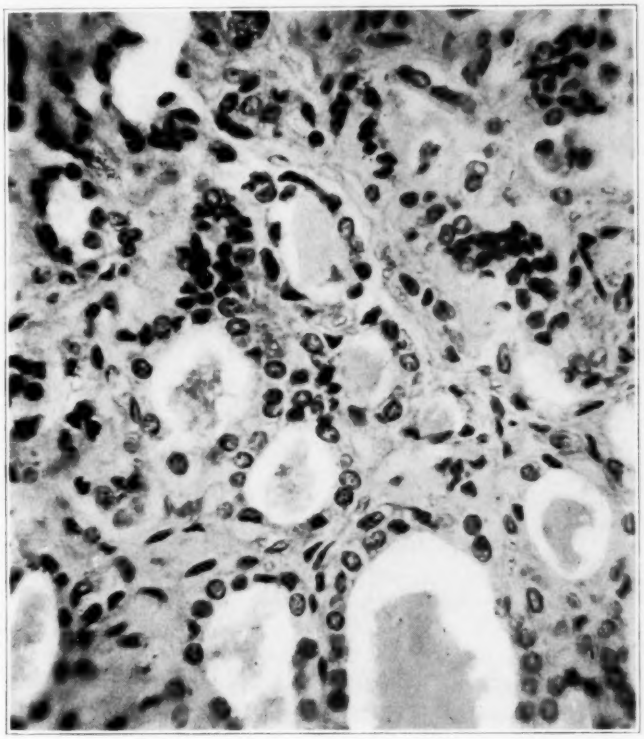

Fig. 3.—Section of the thyroid of a 6 month old mongoloid child. Many acini are enlarged to 200 or 300 microns. The epithelial walls of the acini are irregular, and many cells are dissolved. Many smaller acini are without colloid, and areas of parenchymatous growth can be noted between the acini.

colloid. In some areas there was epithelium without formation of vesicles. The connective tissue was increased and grew profusely in the space around the acini (fig. 3).

CASE 9.—*Mongoloid child aged 7 months* (15 slides).

Although the histologic picture varied slightly in different sections, most of the gland showed striking enlargement of the vesicles, which measured usually from 250 to 300 microns. Between the large vesicles there were observed smaller

ones. They were tightly packed with colloid. The increase in colloid was so striking that the vesicles touched each other and were separated by little connective tissue. In many parts the walls were destroyed, and the epithelial cells floated in the colloid. Other sections showed high epithelium and duplication of the cell walls. The histologic picture was similar to that of true colloid goiter, although the size of the gland as a whole was diminished. In addition to the areas with enlarged follicles there were smaller portions in which the vesicles were not so

Fig. 4.—Section of the thyroid of a 7 month old mongoloid child. All the acini are extremely distended. The average size is from 250 to 300 microns. The acini are tightly packed with colloid. Free colloid was also observed within the spaces. Many of the epithelial walls are destroyed. The picture represents a condition usually seen in colloid goiter.

enlarged. In these regions there was overgrowth of epithelial cells, and the walls consisted of high cylindric epithelium (fig. 4).

CASE 10.—*Mongoloid child aged 9 months* (13 slides).

The slides again showed marked difference in the amount of pathologic change. Many enlarged follicles with high epithelial cells were seen. Enlargement of vesicles up to 550 microns occurred in some sections. Other vesicles showed

extremely flat epithelium, and between the tubules there was an increase in connective tissue, so that the tubules were isolated from each other. There were marked infiltration of colloid into the spaces of the tissue and much cellular growth without formation of follicles (fig. 5).

CASE 11.—*Mongoloid girl aged 10 months.*

In sections of the trachea and the tissue surrounding the trachea, in which the thyroid gland is usually to be seen, there was no thyroid tissue. The only thyroid

Fig. 5.—Section of thyroid of a 9 month old mongoloid child. Enlargement of acini up to 550 microns could be noted. Colloid was observed within the spaces. Note the irregularity in size of the vesicles. The epithelial walls are extremely thin. Between the vesicles there is marked parenchymatous growth without regular formation of vesicles.

seen in this case was a small, displaced piece within the thymus. This consisted of thick strips of connective tissue in which were dispersed typical thyroid vesicles surrounded by large, nucleated epithelial cells; such tubules were rare, however. Figure 6 shows the only area in which some tubules were conglomerated. The other

parts showed only piles of epithelial cells of the thyroid type, without formation of vesicles. There were many red blood cells within the tissue.

CASE 12.—*Mongoloid child aged 13 months.*

Many of the tubules were strikingly enlarged and irregular. Enlargements of from 240 to 450 microns could be noted. Many tubules were confluent, and epithelial folds were floating within the regular lumen. Besides the formed vesicles, the epithelial cells of which showed large round nuclei, there was much growth of irregular epithelial cells. The spaces between many lobes were filled with epithelial cells which did not form vesicles or belong to transverse sections

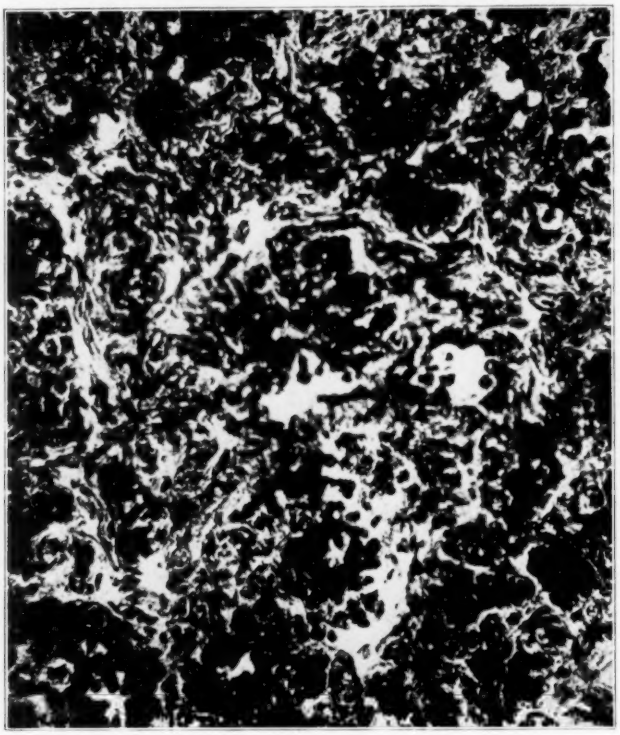

Fig. 6.—Section of the thyroid of a 10 month old mongoloid girl from within the tissue of the thymus. There is irregular parenchymal growth without formation of regular vesicles or production of colloid.

of the tubules. The tubules were filled with pinkish-stained colloid, mostly retracted from the walls. Some areas showed increase in connective tissue, and already there were degenerated cells within these layers (fig. 7).

CASE 13.—*Mongoloid child aged 18 months* (11 slides).

The section of the thyroid showed a large area of medium-sized tubules. The nuclei were round and rich in chromatin. The vesicles were walled with uniform epithelial cells. In other sections, however, there was undoubted abnormal glandular tissue. Large, irregular tubules were observed, which were formed through the

confluence of smaller tubules without colloid or with little vacuolated colloid. Much infiltration with colloid could be seen about acini.

CASE 14.—*Mongoloid girl aged 2 years and 4 months.*

The tubules were mostly enlarged and irregular. The epithelial wall was thin and flat. It consisted of small nucleated cells, which were undoubtedly flattened. The colloid stained deep red and contained many small round cells. Most of the smaller tubules did not have regular walls, but lay in an irregular growth of nucleated epithelial cells. Within the connective tissue there was much homogeneous, red-stained colloid.

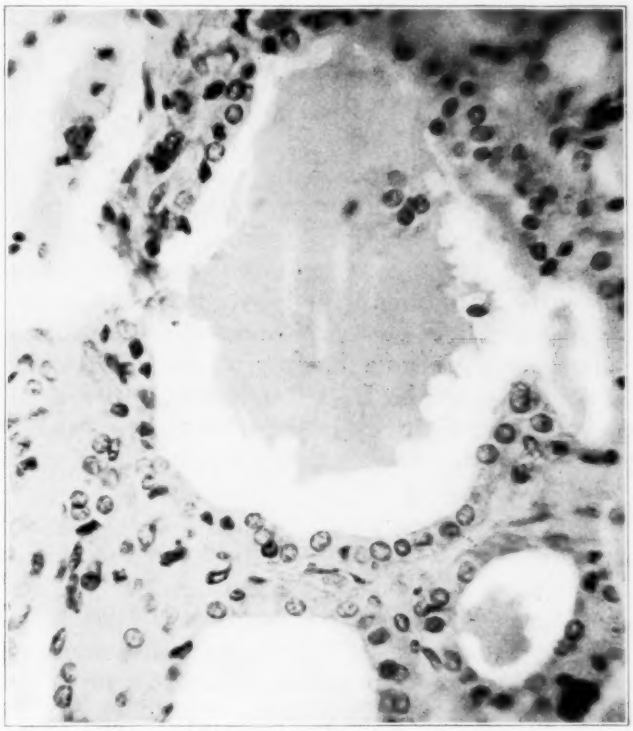

Fig. 7.—Section of the thyroid of a 13 month old mongoloid child. Enlargement of the vesicles from 240 to 450 microns could be noted. The epithelial walls are irregular. Some cells are in good condition, but many are destroyed and show small irregular nuclei. Colloid is present within the vesicles and has infiltrated into the spaces of the glandular tissue.

COMMENT

In summarizing the results of examination of the thyroid gland in 14 cases, it is obvious that in all there were remarkable alterations. It is difficult to understand why there is so much discussion in the literature as to whether there are changes in the thyroid gland in mongolism.

The observations at autopsy reported in the literature are contradictory. After analyzing this literature, I had the impression that it is not worth while to deal at length with the earlier literature. Most of the reports did not give details, and no special autopsy studies were carried out. Most of the autopsy records referred to older children, in whom the condition is complicated. Regressive alterations are much more striking, and it is hard to discover what was the original structure of the thyroid and what were secondary alterations.

Knowledge of pathologic conditions of the thyroid gland, and of the thyroid of infants especially, is recent, and many points are still under discussion. Even in regard to the different types of goiter there are still many contradictory opinions. I shall call attention to only a few publications: those of Wegelin,[3a] Kocher,[4] Gold and Orator[5] and Stahnke.[6]

When one remembers that the goitrous thyroid has been an object of much research for more than thirty years, it is not surprising that the few investigations dealing with the thyroid of persons with mongolism are contradictory. A second factor is that the development of the thyroid during the first years of life is still under discussion.

In the earlier literature Bourneville reported definite changes in the thyroid of mongoloid patients, mostly of a degenerative nature. In recent publications, Gordon[7] and Pennacchietti[8] reported changes similar to those observed in my cases. Pennacchietti called attention especially to the similarity between the thyroid in his case and that seen in cases of goiter in childhood.

Because of the assumption in the clinical part of this study that mongolism must have its origin before birth, I was especially interested in the early stages of alteration. In my opinion the autopsy observations in the youngest mongoloid children deserve the most interest.

I wish to emphasize that after birth the mongoloid organism reaches some kind of equilibrium of the endocrine glands; if the adjustment is not made the child dies early. The older mongoloid infant as a biologic

---

3a. Wegelin, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 1.

4. Kocher, A.: Die histologische und chemische Veränderung der Schilddrüse bei Morbus Basedowii und ihre Beziehung zur Funktion der Drüse, Virchows Arch. f. path. Anat. **208**:86, 1912.

5. Gold, E., and Orator, V.: Struma in Adults, Virchows Arch. f. path. Anat. **252**:671, 1924.

6. Stahnke, E.: Zur Histologie und Klinik jugendlicher Strumen (in Unterfranken), Arch. f. klin. Chir. **125**:193, 1923.

7. Gordon, M. B.: Morphological Changes in the Endocrine Glands in Mongolian Idiocy, with Report of Two Cases, Endocrinology **14**:1, 1930.

8. Pennacchietti, M.: Contributo anatomo-pathologico allo studio della idiozia mongoloide, Endocrinol. e pat. costit. **10**:148, 1935.

being lives like others, but on a lower level. It is logical, therefore, that one sees at autopsies on older patients adjustment of the endocrine glands to the condition of life. No striking abnormalities can be expected.

Pathologic study of the thyroids of 14 children between 9 days and about 2 years of age—most of whom were in the first year of life—gave uniform results. All the thyroids showed histologic signs that were regarded as indicative of hyperactivity or involutional changes in the glands. Development of the glands in regard to the size of the acini, the colloid content, the growth of the epithelium and the development of connective tissue had progressed much further than would be expected. In all cases the thyroid was in a stage that did not correspond with the age of the child.

In order to obtain information as to the difference between the so-called normal thyroid and the thyroid in mongolism, I compared slides of thyroids of children with mongolism with those of thyroids of other children of the same age. In addition, careful studies of the normal anatomic picture of the thyroid at birth and in the first months of life have been made. Wetzel,[9] in a summary of the various studies, stated that the thyroid of infants shows a uniform picture. The vesicles are almost of equal size, and the diameter increases gradually during the first year from 50 to 100 microns. The epithelial walls are formed mostly by cubic or small cylindric epithelium. The colloid in the first year is more liquid than that in adult life.

I cannot agree with Wetzel's statement concerning the uniformity of the vesicles in the so-called normal thyroid. I found inequality in size in all thyroids of 30 infants. However, some uniformity with regard to size and shape is discernible. Enlargement to more than 150 microns and folding of the walls in the first months of life are indicative of pathologic changes. Of much more significance are the lack of formation of acini and an irregular growth of epithelium between the vesicles. The normal acini are walled with regular epithelium. Multiplication of layers of the epithelial wall, diffusion of colloid into the surrounding tissue and formation of large strips of connective tissue between the acini are observations which verify the statement of definite pathologic changes.

In nearly all my cases examination revealed marked enlargement and irregularity in the shape of the tubules. There was also epithelial proliferation between the acini without formation of vesicles or production of colloid. There was striking irregularity in the size and shape of the nuclei. In many cases there was much colloid about the vesicles, in

9. Wetzel, G.: Handbuch der Anatomie des Kindes, Munich, Germany, J. F. Bergmann, 1936.

which epithelial cells were scattered. The connective tissue showed an irregular, abundant growth.

When I attempt to arrange these observations to form a pathologic diagnosis the difficulties are remarkable. However, this is true of the pathology of all diseases of the thyroid. Boyd [10] has given this fact expression. I have mentioned already that the changes in mongolism remind one of pictures seen in goiter. Boyd, however, pointed out:

> From the pathological point of view the present method of classifying goiters is far from satisfactory. Goiters are usually divided into three main groups, which are regarded as being entirely distinct entities. The first is known as simple or endemic (colloid) goiter, the second as adenomatous goiter, the third as exophthalmic goiter.
>
> A pathological classification should attempt to give some idea of the actual condition of the thyroid. The more one sees of goiter, the less is one inclined to subdivide the lesions too minutely. If the reader will take a series of cases and study a number of blocks from each thyroid, he will be surprised to find how varied are the lesions in any one gland. A simple or colloid goiter is supposed to be one in which the gland is in a completely resting condition, and yet evidence of hyperplasia can nearly always be found if it is looked for. Exophthalmic goiter is characterized by a general hyperplasia, but colloid areas indicating involution are found in all but the most fulminating cases. Finally, adenomata when well developed form a striking gross feature, but more or less complete localization and encapsulation of areas can be found in glands in which the enlargement to the naked eye appears to be quite diffuse. It is not too much to say that quite often in a single section one can see areas characteristic of exophthalmic goiter, of colloid goiter, and of adenomatous goiter. The differences are quantitative rather than qualitative. The morbid anatomical picture depends upon the balance between the processes of hyperplasia and involution, upon the extent to which the hyperplasia has gone before involution has set in, and upon the degree of localization of the hyperplastic and involutionary processes.

In a study of pathologic conditions of the thyroid, Murray [11] distinguished two types of changes: exophthalmic goiter and fibrosis of the thyroid. He observed that the latter is characterized by decrease in alveoli and a large amount of young cellular fibrous tissue.

> It thus seems evident that the development of thyroidal fibrosis in exophthalmic goiter by lessening the over-activity of the gland leads to a subsidence of the symptoms, which, if the fibrosis and atrophy progress enough, are replaced by those of myxedema.

In patients with mongolism I observed both types of goitrous alterations, the colloid and the parenchymatous goiter. This means that the histologic picture of the thyroid in mongolism is indicative of a condition

---

10. Boyd, W.: The Pathology of Internal Diseases, ed. 2, Philadelphia, Lea & Febiger, 1935.

11. Murray, G. R.: The Goulstonian Lectures on the Pathology of Thyroid Gland, Lancet **1**:667 (March 11); 747 (March 18) 1899.

of the thyroid similar to goiter. However, it differs in one important point. The thyroid in patients with mongolism is not enlarged as a whole, but is diminished in size and weight. As far as I was able to obtain exact measurements, I observed that the weight of the thyroid was very small. This is especially true of the thyroid of older children and adults. At a recent autopsy on a man aged 32 the thyroid weighed only 7 Gm. The expected weight is about 30 Gm.[12] Therefore, one must face the fact that there are signs on the one hand of hyperactivity and, on the other, of degeneration. This makes the explanation of this condition difficult.

Cretinism is said to be due to lack of function of the thyroid. Knowledge of the hypofunction of the thyroid, especially of complete athyroidism, is well established through the fact that the surgical removal of the whole thyroid gives a salient demonstration of experimental athyroidism. When this cause of cretinism became apparent, the temptation was great to relate some signs of mongolism to lack of a thyroid. The halting of growth, the peculiar appearance, the pug-shaped nose, the big, protruding tongue, the dry and scaly skin, the stout figure, the underdevelopment of the gonads and the retardation of mental development all seem to be more or less the same in both conditions. This led to frequent attempts to treat mongoloid children with thyroid substances. However, the clinical differences are striking, and many authors have tabulated differences between mongolism and cretinism (Siegert, Tredgold and recently Higgins, cited by Means). With regard to the structure and function of the thyroid in mongolism one faces a very complicated situation.

Mongolism is completed before birth. The large experience in cases of congenital athyroidism and cretinism makes it probable that during pregnancy the thyroid of the mother carries out the function of the thyroid for both mother and child. The thyroid of the embryo is thought to have no function. Even in conditions of complete congenital lack of thyroid, athyroidism gives rise to clinical symptoms not earlier than about two months after birth. The diagnosis of cretinism cannot be made at the time of birth, and it becomes obvious not sooner than the second or third month of life. In contrast, mongolism is present at birth, and this fact is conclusive evidence that lack of thyroid cannot be the essential cause of mongolism.

On the other hand, nothing is known of the influence of hyperactivity of the thyroid on the developing human embryo. It is well known that women with exophthalmic goiter may become pregnant and

12. Rösle reported the weight of the thyroid in 3 patients with mongolism: in a child aged 7 weeks, 2 Gm.; in a child aged 16 months, 2.4 Gm., and in a child aged 9½ months, 1.2 Gm. (Wachstum und Altern: Ergebn. d. allg. Path. u. path. Anat. **20**:369, 1923).

give birth to a normal infant. There is no record in the literature that a woman with obvious exophthalmic goiter was delivered of a mongoloid child; with the great interest which has always been given to this condition, such an occurrence would be reported.

Stoeltzner [13] reported 3 instances in which the mother had a myxedematous condition during pregnancy and was delivered of a mongoloid child.

It is important to make pathologic studies in cases of stillbirths in which the mother is suffering from exophthalmic goiter or a myxedematous condition. Many mongoloid infants die a few days after birth or are even premature. It is suspected that some stillborn children may be mongoloid. Only such a study of stillborn and living children of mothers suffering from thyroid disease can decide whether or not the condition of the mother's thyroid plays an important role.

As long as one is forced to draw conclusions about pathologic function from histologic study, one is able only to guess what pathologic process has taken place in mongolism.

Pathologic study shows that signs of hyperactivity can be seen histologically in children with mongolism at an early age. There is secondary proof that late degenerative alterations play an important role. In view of this situation, the only possible conclusion is that early activation of the thyroid has taken place. The thyroids which one can study in cases of mongolism are the product of activation and secondary exhaustion. In view of the fact that mongolism is completed before birth, the pathologic disturbance must have occurred early in embryonic development.

The fundamental problem is: Are there any clues from experimental studies or from clinical experience that prenatal thyroidism may play an important role in the peculiar formation of the skull and the irregularities in ossification?

Many experimental studies have dealt with the results of administration of thyroid to growing animals. In order to have a basis for the following conclusions, I must refer more extensively to these investigations.

During the years 1909 to 1914, Gudernatsch, of New York, demonstrated the influence of the thyroid on growth and differentiation through feeding experiments on tadpoles. These classic experiments had definite results and laid the foundation for knowledge of the influence of the thyroid gland on the growing organism. The experiments have been repeated by other outstanding investigators. Experiments with feeding thyroid or derivatives of this gland have shown that the development of

13. Stoeltzner, W.: Zur Aetiologie des Mongolismus, München. med. Wchnschr. **66**:1493, 1919.

the body is accelerated in some direction, but the different organs do not keep pace equally in their development, so that the cooperation of the organs, which is essential for normal life, is disturbed. Every organ is stimulated to a different degree. The bones are especially sensitive to administration of thyroid. Gudernatsch emphasized that administration of thyroid leads to early ossification in the growing organism, and this makes further growth impossible through early maturing of the tissue. It is interesting that Romeis described especially the effect of thyroid on development of the skull of larvae of Rana. The shape of the skull of a normal larva of Rana temporaria is similar to the curve of the pointed end of an egg. In larvae treated with thyroid this line is affected by, and flattened in proportion to, the feeding (the higher the dosage the flatter the line). This line becomes more like the curved end of the egg, and in some instances the frontal boundaries of the head even become straight. The heads of typical tadpoles treated with thyroid appear broader than normal. This fact is caused partly through particular changes in the skull; the nasal part of the skull, especially, is much shorter than normal, so that the eyes lie farther to the front than in normal animals. The size of the eyes does not participate in the reduction of the other organs, so that the eyeballs protrude more and increase the peculiarity of the appearance of these animals. The edge of the eye, especially the lateral portion, is more marked than in normal larvae of the same age.

Administration of thyroid also influences development of the tongue, the jaws and the lips. The upper jaw stops in further development, and some animals are unable to shut their mouths. The animals lie always with wide-open mouths. The skin is leathery and much more resistant than that of normal animals, owing to hyperdevelopment. The development of the extremities in the first stages is more rapid, but it stops earlier than usual. The final effect is shortening of the extremities.

It is surprising how similar the morphologic changes are to those already described as occurring in mongolism. With some qualifications, it may be permissible to speak of the observations in frogs as "experimental mongolism."

These experiments also pointed the way to distinguishing of two aspects of normal development—differentiation and growth. Although these two tendencies are usually correlated, it is possible to separate them. In pathologic conditions there occurs a break in their normal relationship. The thyroid has a striking influence on differentiation, and the effect of early differentiation consists in lack of growth, particularly dwarfism.

It is impossible to report on all these interesting experiments. The extensive literature on the subject, especially the publications of Guder-

natsch, Romeis, Abderhalden, E. R. Hoskins, Osborne, T. B. Robertson and W. Schulze, may be mentioned.[14]

Summarizing these experiments on animals, one may say that hyperadministration of thyroid to a growing organism has the effect of irregular, early ossification. Especially interesting are the changes in skull and nose, which consist of flattening and lack of later differentiation; the influence on the growth of the tongue; the leathery skin, and the final effect of early ossification, resulting in dwarfism and microcephaly. Gudernatsch summarized the results of his research as follows:[15]

1. The thyroid has the power to excite differentiation, but it lacks power to cause growth.

The thyroid calls forth differentiation, whether the animals be small or large and without regard to the standard minimum size, necessary for the final change. It must possess an agent for stimulating differentiation which other foods do not possess. That the thyroid also possesses a power which prevents growth is not evident. The suppression of growth may merely be incidental, for rapid differentiation does not allow growth.

2. The thymus has the power to stimulate growth, but lacks the power to excite differentiation.

A comparison of the experiments described and the pathologic picture in mongolism suggests that a temporary excess of thyroid may have affected the normal differentiation of the embryo.[16]

SUMMARY

The question of the presence of hyperthyroidism during the embryonic development of mongoloid children is important. Facts seem to indicate that hyperthyroidism during the prenatal period is a cornerstone on which rests the explanation of mongolism.

Pathologic study of the thyroid in cases of mongolism reveals that alterations are invariable. These consist in involutional changes: Distention of acini, filled with colloid and composed of low epithelium; folding and confluence of acini; diffusion of colloid in the surrounding

14. For the complete literature, see the publication by Gudernatsch, in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1933, vol. 3.

15. Gudernatsch, J. F.: Feeding Experiments on Tadpoles: II. A Further Contribution to the Knowledge of Organs with Internal Secretion, Am. J. Anat. **15**: 431, 1914.

16. After having finished this study, I learned that Clark, of Edinburgh, Scotland, has dealt with mongolism in four papers. (Clark, R. M.: The Mongol: A New Explanation, J. Ment. Sc. **74**:265 and 739, 1928; **75**:261, 1929; **79**:328, 1933). He declared that mongolism is "fetal hyperthyroidism ceasing at birth." Clark's papers are merely speculative; he did not support his ideas by clinical or pathologic investigations. Although my own study supports the hypothesis of fetal hyperthyroidism in some ways, I do not believe that Clark's theory is sufficient to explain mongolism. I shall show in the next paper how complicated the endocrine disorder in mongolism is.

spaces; overgrowth of epithelium in thick piles, like an adenomatous growth, without formation of new vesicles; changes in the form and shape of the epithelium; increase in stroma, and degeneration of glandular tissue.

It is impossible to draw definite conclusions from the histologic picture as to the functional condition of the thyroid. However, the changes seen in mongolism differ from those usual in myxedema, and the resemblance to conditions observed in the various types of goiter is suggestive of a temporary stage of hyperfunction or dysfunction. It is not known whether the thyroid in mongoloid infants worked too effectively or too early. It is more probable that the condition results from other influences which affected the embryo. There may be the influence of the maternal thyroid or some other stimulating factor resulting from unbalance of the maternal endocrine glands. There may be also stimulation through another endocrine gland in the mongoloid organism itself. One cannot decide this question at present; the problem should be the object of experiment and examinations on a large scale.

The histologic picture of the thyroid gland in mongolism reminds me of the histologic changes seen in cases of pituitary disease and in experiments with this gland. The parenchymatous hyperplasia of the thyroid produced through administration of extracts containing the so-called thyrotropic hormone derived from the anterior lobe of the pituitary has been studied thoroughly in recent years (Collip, Hertz and Oastler, Krogh, Lindbergh, Loeb and others).[17] I shall present the changes in the pituitary body associated with mongolism in another paper.

17. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937.

CEREBRAL CIRCULATION

II. REACTION OF PIAL ARTERIES TO INCREASE IN BLOOD PRESSURE

MOGENS FOG, M.D.
COPENHAGEN, DENMARK

Investigations by Fog [1] and Forbes, Nason and Wortman [2] have demonstrated that the pial arteries react to a fall in blood pressure by dilatation. This reaction was shown to be independent of the way in which the fall in pressure was produced. It was noted also by these authors that the same arteries react to a rise in blood pressure by constriction, but no detailed description of the latter reaction was given. During recent experiments with epinephrine,[3] I have made observations which confirmed these earlier findings, but in view of the various conclusions reached by other investigators, it seemed desirable to carry out further experiments, using the method of direct observation.

Heretofore, conclusions as to cerebral vascular reactions have been drawn largely from data obtained by indirect methods. By all such methods the changes in caliber of the vessels are inferred, not observed. Therefore, even if data were obtained under controlled conditions it would be impossible to say precisely which vessels, or vessels of what size, participate in the reaction.

By the use of indirect methods, Schultén,[4] Falkenheim and Naunyn [5] and Bayliss and Hill [6] recorded an increase of intracranial volume or of pressure, and the workers last mentioned concluded that passive dilatation of the cerebral vessels occurs.

From the Medicophysiologic Institute of the University of Copenhagen.

This investigation was aided by a grant from the Rockefeller Foundation.

1. Fog, M.: (*a*) Om piaarteriernes vasomotoriske reactioner, Danish Dissert., 1934; (*b*) Cerebral Circulation: Reaction of Pial Arteries to Fall in Blood Pressure, Arch. Neurol. & Psychiat. **37**:351 (Feb.) 1937.

2. Forbes, H. S.; Nason, G. I., and Wortman, R. C.: Cerebral Circulation: Vasodilation in Pia Following Stimulation of Vagus, Aortic and Carotid Sinus, Arch. Neurol. & Psychiat. **37**:334 (Feb.) 1937.

3. Fog, M.: Cerebral Circulation: I. Reaction of Pial Arteries to Epinephrine by Direct Application and by Intravenous Injection, Arch. Neurol. & Psychiat. **41**:109 (Jan.) 1939.

4. von Schultén, M. W.: Arch. f. Ophth. **30**:59, 1884.

5. Falkenheim, H., and Naunyn, B.: Arch. f. exper. Path. u. Pharmakol. **22**:261, 1887.

6. Bayliss, W. M., and Hill, L.: J. Physiol. **18**:334, 1895.

Biedl and Reiner[7] made long-continued measurements of the systemic arterial pressure and of arterial pressure in the circle of Willis. In a number of instances they demonstrated spontaneous fluctuations in pressure, opposite in direction, in the two systems. This difference, they claimed, was indicative of an independent vasomotor function on the part of the cerebral vessels, which were thus capable of responding to a rise in blood pressure by constriction.

Heymans and Bouckaert,[8] experimenting on dogs, used an isolated head preparation supplied with blood from another animal and connected with the trunk only by the spinal cord and vasosympathetic nerves. They obtained evidence of dilatation of the cephalic vessels in response to a rise in systemic arterial pressure. This dilatation they thought was caused by a reflex. But no information was obtained on the direct effect on the vessels of the rise in pressure.

In contrast to the limited number of investigations on the effect of "simple" hypertension, studies on the cerebral vessels during the hypertension caused by epinephrine have been numerous. These were reviewed recently.[9]

As I have pointed out,[3] the difference in the conclusions arrived at may have been due partly to the different methods employed and partly to the fact that the smaller and the larger arteries do not always react in the same manner.

My object in the present investigation was to study in detail the response of the smaller pial arteries (arterioles) to a rise in arterial pressure. The rise in pressure was produced by various means: intravenous injections of epinephrine, stimulation of the splanchnic nerves and compression of the abdominal aorta. Only arteries of less than 50 microns in diameter were studied, for it had been learned that these vessels are not influenced by the direct chemical action of epinephrine.[10]

METHOD

The same anesthetic and the same methods of recording arterial diameter, blood pressure and the like were used as in earlier investigations.[11] The injections of solutions of epinephrine hydrochloride were usually intravenous, but sometimes intra-arterial. Doses of from 10 to 100 micrograms, in solutions of 1:10,000 or 1:100,000, were given usually during periods of from one-half to one minute. In

7. Biedl, A., and Reiner, M.: Arch. f. d. ges. Physiol. **79**:158, 1900.

8. Heymans, C., and Bouckaert, J. J.: Compt. rend. Soc. de biol. **99**:1871, 1928.

9. Bouckaert, J. J., and Jourdan, F.: (*a*) Arch. internat. de pharmacodyn. et de thérap. **54**:109, 1936; (*b*) Rev. belge sc. méd. **8**:12, 1937.

10. (*a*) Forbes, H. S.; Finley, K. H., and Nason, G. I.: Cerebral Circulation: Action of Epinephrine on Pial Vessels, Arch. Neurol. & Psychiat. **30**:957 (Nov.) 1933. (*b*) Fog, footnotes 1a and 3.

11. Fog, footnotes 1 and 3.

10 cats instillations from a buret into the cardiac end of the external jugular vein were made during a period of from one to nine minutes, in order to obtain a prolonged effect of epinephrine. The maximum dose was 0.5 mg. Experiments with 9 cats were carried out with artificial respiration. The remaining experiments were performed with spontaneous respiration.

The splanchnic nerve was isolated either through laparotomy or retroperitoneally and was stimulated by faradic current, with from six to eight shocks per second. Care was taken that the bipolar electrode was placed peripheral to the branches to the adrenal bodies.

Compression of the aorta was performed by means of a loop led around it above the celiac artery, the aorta being exposed from the dorsal side.

EXPERIMENTS

One hundred and thirty experiments were performed on 22 cats. The blood pressure was raised in 27 instances by stimulation of the splanchnic nerve or by aortic compression and in 79 instances by epinephrine. The results are summarized

TABLE 1.—*Data on Reaction of Pial Arteries to Increase in Blood Pressure*

1. Blood Pressure Raised by Stimulation of Splanchnic Nerves or by Compression of Aorta

Reactions of Pial Arteries	No. of Cases	Average Change in Diameter, Microns	Percentage of Rise in Blood Pressure
Constriction	16	5	30
No reaction	10	0	12
Dilatation	1	3	29

2. Blood Pressure Raised by Injections of Epinephrine

Reactions of Pial Arteries	No. of Cases	Average Change in Diameter, Microns	Percentage of Rise in Blood Pressure
Constriction	41	7.5	43
No reaction	25	0	52
Dilatation	13	5.8	102

in table 1. In 24 instances the blood pressure was below 50 mm. of mercury before the experiment started. This group will be considered separately.

It can be seen from the figures in the table that the reactions of the arterioles were similar, regardless of whether the blood pressure was raised by epinephrine or in other ways (figs. 1 and 2). Usually the arterioles became constricted; sometimes they did not change, and rarely they dilated during the rise in pressure. It should be kept in mind that failure to dilate when the intravascular pressure rises sharply indicates an active process (or change in tonus of the walls of the vessels); otherwise they would yield to the change in internal pressure. One must conclude, therefore, that in 92 of 106 experiments the pial arteries showed an "active" response to the rise in blood pressure. Only in 14 of the 106 experiments were the responses "passive."

In a detailed analysis of the results, great variations in the degree and direction of the changes in diameter were revealed, not only when 2 experimental animals were compared but also in a number of

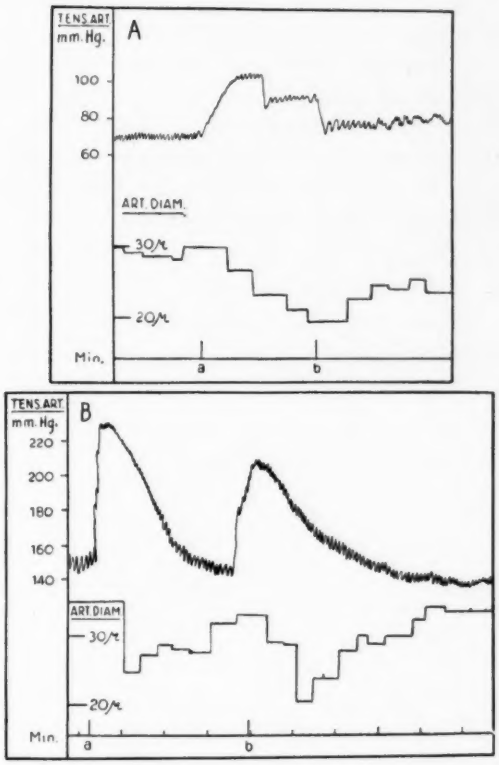

Fig. 1.—Reactions of an artery during increase in blood pressure. In *A*, *a* to *b* indicates stimulation of the splanchnic nerve. In *B*, *a* to *b* indicates instillation of epinephrine.

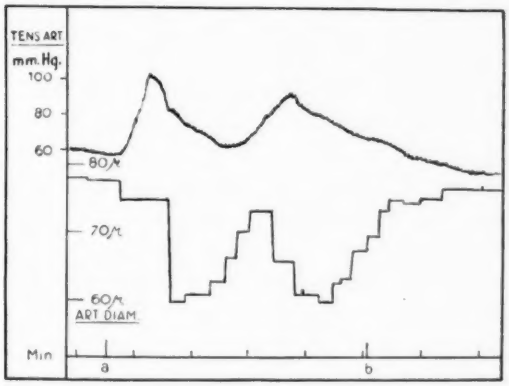

Fig. 2.—Reaction of an artery during increase in blood pressure. In the graph, *a* to *b* indicates changes in pressure in an isolated carotid sinus sac.

experiments on the same cat. These differences, however, were found to be dependent largely on two factors: the varying amount of rise in blood pressure and the varying level of the initial pressure.

The significance of the first-mentioned factor is apparent from table 2, which comprises both groups of experiments from table 1. Most frequently hypertension of less than 20 per cent above the original level of pressure will provoke no reaction of the arteries. A rise of more than 20 per cent usually produces constriction (53 cases) or no reaction (24 cases), i.e., an increase in the constrictor tone of the arterial walls. Dilator responses are more frequent the higher the hypertension and the more rapidly it is provoked. This may explain the fact that dilatation occurred thirteen times when epinephrine was given, and only once when the blood pressure was raised less by other means.

TABLE 2.—*Significance of Amount of Rise in Blood Pressure on Reaction of Pial Arteries*

	Contraction				No Reaction			Dilatation			
Rise in Blood Pressure, %	No. of Cases	Initial Blood Pressure, Mm. of Mercury	Initial Diameter, Microns	Reaction of Arteries, %	No. of Cases	Initial Blood Pressure, Mm. of Mercury	Initial Diameter, Microns	No. of Cases	Initial Blood Pressure, Mm. of Mercury	Initial Diameter, Microns	Reaction of Arteries, %
<20	4	120	22	−15	11	118	22	2	108	36	+16
20-100	43	98	26	−22	22	104	25	4	107	21	+18
>100	10	60	31	−40	2	85	27	8	85	29	+16

If the blood pressure of a cat is reduced from a high level (from 110 to 140 mm. of mercury) to a lower level (from 70 to 90 mm. of mercury), a given dose of epinephrine will cause a greater rise in pressure from the low than from the high initial level. Also, the pial arterioles will show more active constriction after the pressure has been lowered. To study the influence of initial arterial pressure on the reactions of the vessels, the dose of epinephrine must be reduced, so that the rise in blood pressure will be no greater from a low than from a high level.

Figure 3*A* and *B* shows the results of such a procedure. The experiment was repeated several times with different animals, with similar results. It is obvious that in two trials showing the same rise in blood pressure, but from different initial levels, the constriction is much more pronounced when the initial pressure is low than when it is high.

In 1 animal identical rises in blood pressure were produced once before and again during the inhalation of carbon dioxide (6 per cent). The initial blood pressure was practically the same in each case. The arterioles dilated by the carbon dioxide appeared to constrict more

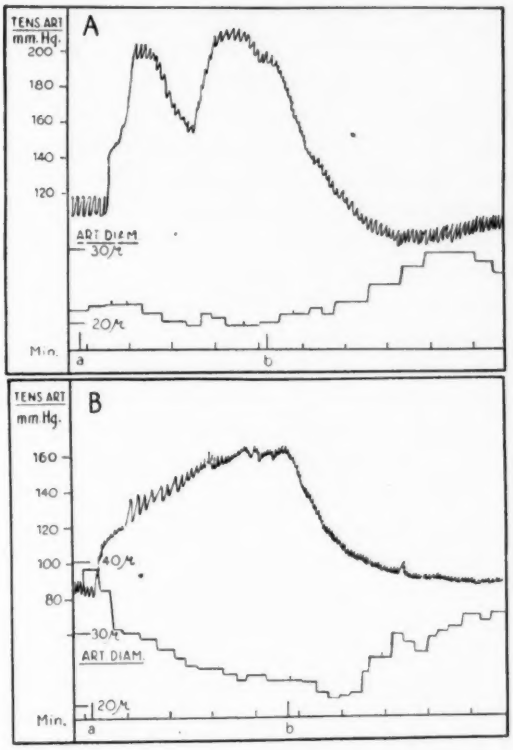

Fig. 3.—*A*, reaction of an artery during increase in blood pressure from a high tension level. In this graph and in the graph shown in *B*, *a* to *b* indicates instillation of epinephrine.

B, reaction of the same artery as that in *A* during increase in blood pressure from a low tension level.

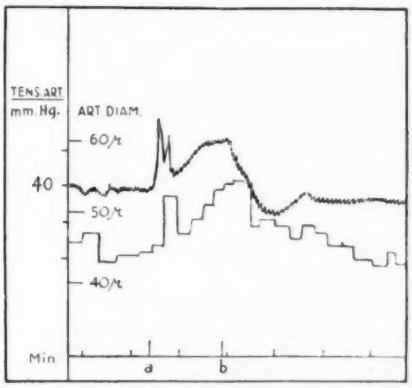

Fig. 4.—Passive reaction of an artery during rise in blood pressure from a tension of 40 mm. of mercury. In this graph, *a* to *b* indicates stimulation of the splanchnic nerve.

in response to the rise in pressure than they had done when not so dilated. Further investigation of the subject has not yet been carried out.

In 2 animals (not mentioned before) the cervical portion of the sympathetic trunk and the vasosensory nerves (from the carotid sinus and aorta) were studied to learn what influence they may have on the arterial reaction to hypertension. It was found that a rise in blood pressure caused the same degree of constriction before and after bilateral section of all postganglionic fibers of the superior cervical ganglion. Then the vagus, depressor and carotid sinus nerves were cut on both sides. Both common carotid arteries were temporarily compressed to make sure that the denervation was complete; no rise in systemic blood pressure resulted. The blood pressure was now raised repeatedly, and each time the pial arterioles constricted as usual.

The group of experiments in which the initial blood pressure was below 50 mm. of mercury will now be considered. In these cases, during the rise in pressure the arterial walls were seen to dilate passively in 21 of 24 trials. This occurred regardless of whether epinephrine, stimulation of the splanchnic nerve or aortic compression was used. In 1 case there was no reaction; in 2 cases constriction was seen. It will be seen from figure 4 that the changes in caliber of the arterioles in this group in almost every instance bore a direct, not an inverse, relation to the changes in blood pressure. It seems as though under these conditions of abnormally low pressure all active tonic regulation by the arterial walls had vanished.

COMMENT

The results of the present series of experiments support the opinion, previously advanced, that epinephrine exerts no direct chemical influence on pial arteries of less than 50 microns in diameter.[3] The results demonstrate, furthermore, that these vessels respond by active constriction to a rise in intravascular pressure. With a normal level of blood pressure (from 110 to 140 mm. of mercury) the constriction in response to hypertension is slight, but since there is no dilatation, one must suppose that an increase in tonus of the smooth muscle fibers in the wall of the vessel has taken place. There are limits, however, to this tonic regulation, for large, sudden rises in pressure will dilate the vessels and when the blood pressure is extremely low all active regulation seems to be lost.

When these findings are correlated with the vascular reactions to a fall in blood pressure,[12] one must conclude that during a normal level of blood pressure the pial arteries assume a minimum size, below which

12. Fog.[1] Forbes, Nason and Wortman.[2]

they seem never to be much reduced. This tonic regulation may play an important part in the maintenance of a steady flow of blood through the brain. The concept of Biedl and Reiner [7] that the resistance of the cerebral circulation is regulated through fluctuations of the blood pressure is confirmed by the findings reported in this paper.

This independent tonic regulation must be taken into consideration when studies of the action of epinephrine on the pial vessels are to be evaluated. As the hormone has no direct influence on the small pial arteries, it is conceivable that any constriction observed with intravascular administration is due to the simultaneous hypertension. Arteries larger than 70 microns in diameter react in the same way toward epinephrine and toward hypertension.[3]

It has been observed by other workers [10a] that when epinephrine is injected into the carotid artery the larger pial arteries often show the following reactions: brief constriction, followed by dilatation when the blood pressure rises; then constriction again, beginning sometimes before the pressure reaches its peak and continuing while the pressure falls to its initial level. When epinephrine was injected into a vein the rise in pressure was usually greater, and then dilatation was the chief response of the pial arteries. It is probable that in this case the mechanical thrust, caused by the sharp rise in intravascular pressure, overwhelmed both the arterial constrictor reaction to hypertension and the constrictor action of epinephrine.

This effect is in accordance with the results obtained by Riser and his co-workers.[13] When large doses of epinephrine were injected intravenously, dilatation of the pial arteries occurred. Intracarotid administration was without effect in 10 dogs and produced only small contractions in 2 cats. On the other hand, there was a marked constrictor action of epinephrine when it was given during a low level of blood pressure (faint heart action and reduced amplitude of pulse pressure).

It is still a question what mechanism causes the arterial reaction to changes in internal pressure. Since the changes in caliber occur regardless of whether the cervical portion of the sympathetic trunk or the vasosensory nerves from the aorta and carotid sinus are intact or severed, it is natural to assume an intracranial regulation. Recent experiments [2] have suggested that this may be ascribed to a local reaction of the smooth muscle of the arterial wall.

SUMMARY

Rises in arterial pressure, whether produced by epinephrine, by stimulation of the splanchnic nerves or by compression of the aorta,

13. Riser, M.; Mériel, P., and Planques: Encéphale **26**:501, 1931. Riser, M., and Sorel, R.: Presse méd. **38**:1073, 1930.

all provoke the same type of reactions in the pial arterioles. The usual response of these vessels to a rise in pressure is by constriction.

Sometimes no change in caliber occurs. This indicates that in these cases also an increase in tonus of the walls of the vessels has taken place. Without such active change in the walls the sudden rise in pressure would cause passive dilatation.

It is found that the arterioles constrict more markedly to a rise in pressure if the initial blood pressure is moderately low (from 60 to 90 mm. of mercury). Yet the caliber of the vessels is never reduced much below that observed during a normal level of pressure.

A large, sudden rise in pressure may overcome the power of the artery to constrict and cause passive dilatation. This is the rule when the initial blood pressure is below 50 mm. of mercury.

CONCLUSION

It appears that changes in intravascular pressure cause changes in the physiologic state (tonus) of the walls of the pial arteries—a fall in pressure causing relaxation and a rise in pressure contraction of the arterial muscle fibers.

This tonic regulation persists immediately after bilateral section of the cervical portion of the sympathetic trunk and bilateral section of all the vasosensory nerves from the aorta and carotid sinus. The mechanism by which the tonus of these vessels is regulated is not yet established.

BODY BUILD IN SCHIZOPHRENIA, WITH SPECIAL REGARD TO AGE

H. GRAY, M.D.
AND
J. G. AYRES, M.D.
SAN FRANCISCO

AIMS

Any disease so frequent, so often difficult to diagnose and so grave as dementia praecox is worth attack even by the undramatic study of build. Psychiatrists record intently many physical and laboratory findings which are customary and indeed useful in medical practice but only too often are of no aid in the diagnosis of mental disease. On the other hand, they care little for studies of build and constitution, although these on the whole support the ancient belief that relations between body and mind can be detected and used. In studies of build crucial experiments or dramatic deviations from the normal are rare, leaving the alternative of comparisons between averages for moderate abnormalities. This alternative is not alluring, partly because it is tedious and partly because medical science has lagged behind other sciences in respect to the advances in applied mathematics. Medical statistics have often been labor lost—unreliable or even wrong—owing to the smallness of the group of subjects and ignorance of the variability and of the error of sampling. Patients are needed in sufficient numbers to permit subdivision and comparison by sex, race, age and diagnosis. Toward this end a series of studies were begun in 1927 with persons with manic-depressive, schizophrenic and finally alcoholic, arteriosclerotic and syphilitic psychoses, and with convicts of approximately like racial mixture and economic class as controls.

The literature has been surveyed, and 100 new cases each have been reported elaborately in monographs of 206 and 347 pages, respectively, by Schmidt [1] in 1929 for Danes and by Plattner [2] in 1932 for Swiss.

From the Medical Clinic, Stanford University School of Medicine, San Francisco; and the Behavior Research Fund, Illinois Institute for Juvenile Research, Chicago.

1. Schmidt, M.: Körperbau und Geisteskrankheit: Eine anthropologisch-klinische Untersuchung zur Beleuchtung des psychiatrischen Konstitutionsproblem, in Foerster, O., and Wilmanns, K.: Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie, Berlin, Julius Springer, 1929, no. 56, p. 206.

2. Plattner, W.: Körperbau-Untersuchungen bei Schizophrenen, Arch. d. Julius Klaus-Stiftg f. Vererbgsforsch. (supp.) **7**:347, 1932.

The general aspects need therefore not be reviewed in this report.[3] The present purpose is to record and discuss observations on 328 schizophrenic patients in Illinois; this series covers different racial material and furthermore is important because three times as large as any series so far reported, so that it can be subdivided into groups still large enough to allow statistical study.

While subgrouping by diagnosis is our main object, that must be deferred to a subsequent paper. Here we shall examine, among schizophrenic subjects, the importance of considering changes in measurements of body build during adult life, which has recently been insisted on by several writers: Hrdlička (1925), Ruger and Stoessiger[4] (1927), Elderton and Moul[5] (1928), Reed and Love[6] (1932), Ruger and Pearson[7] (1933), Gray[8] (1934) and Hrdlička[9] (1936).

MATERIAL

The subjects were patients with schizophrenia (dementia praecox) at the Illinois state hospitals at Chicago, Elgin and Peoria.[10] All were men aged from 20 to 80. The findings will be presented in toto and also subdivided into groups according to age. Observations were made from November 1927 to January 1929. Persons suffering from any congenital defect or acquired deformity, or who were rickety, syphilitic, tuberculous or afflicted otherwise in a manner likely to affect anthropometric characters were excluded by intent. A more important selection was caused by the absence of active "workmen" outdoors on the farm, which biased the material in the direction of deterioration.

3. In the interest of brevity a detailed bibliography is not included here. The papers listed include references to some of the authors mentioned in the present paper and to many others not here discussed.

4. Ruger, H. A., and Stoessiger, B.: On the Growth Curves of Certain Characters in Man, Ann. Eugenics **2**:76 (April) 1927.

5. Elderton, E. M., and Moul, M.: On the Growth Curves of Certain Characters in Women and the Interrelationship of These Characters, Ann. Eugenics **3**:277 (Oct.) 1928.

6. Reed, L. J., and Love, A. G.: Biometric Studies on United States Army Officers: Somatological Norms, Correlations, and Changes with Age, Human Biol. **4**:510 (Dec.) 1932.

7. Ruger, H. A.: On the Interrelationship of Certain Characters in Man (Males), Ann. Eugenics **5**:59 (Jan.) 1933. Ruger, H. A., and Pearson, K.: On the Interrelationship of Certain Characters in Man (Males), ibid. **5**:364 (Oct.) 1933.

8. Gray, H.: Body-Build in Illinois Convicts with Special Reference to Age, J. Crim. Law & Criminol. **25**:554 (Dec.) 1934.

9. Hrdlička, A.: Growth During Adult Life, Proc. Am. Philos. Soc. **76**: 847, 1936.

10. Drs. Edmund A. Foley, Ralph T. Hinton and G. A. Zeller effected arrangements in these institutions.

The proportion of patients thus lost to observation we could not determine. There were 328 patients, all white. The severity of the psychosis was not considered; but, as already remarked, the patients undoubtedly suffered from greater physical deterioration than a series totally unselected would have. Tube feeding, furthermore, contributed to undernutrition in some, but in how many we cannot state.

Duration of the psychosis and of the stay in the hospital were not considered. In this paper all forms of the disease will be considered together, discrimination between the four clinical classes, catatonic, hebephrenic, paranoid and simple, being left for a separate paper.

The relative frequency of schizophrenia, as compared with other psychoses in the material may be seen in table 1, together with figures from other sources. Especially to be noted are the rarity of definitely diagnosed manic-depressive psychosis and relative frequency of the four forms of schizophrenia. The startling fluctuations of the rates of incidence will not be analyzed here.

TABLE 1.—*Relative Frequency of the Psychoses*

Psychosis		Illinois	Some Low/High Rates Elsewhere
Manic-depressive, definite		3.6	2.5 in Breslau, Germany (Georgi) 16.0 in 77 U. S. hospitals (Pollock and Furbush)
Schizophrenic, simple	5.3		
catatonic	7.7		
paranoid	8.6		
hebephrenic	43.6		
all forms		65.2	21.9 in Philadelphia (Strecker and Ebaugh) 44.7 in Graz, Germany (Michel and Weeber)
Alcoholic		9.0	2.3 in 26 states (Pollock and Furbush) 11.4 in Philadelphia (Strecker and Ebaugh)
Arteriosclerotic and senile		9.6	12.1 in 77 U. S. hospitals (Pollock and Furbush) 21.7 in Philadelphia (Strecker and Ebaugh)
Syphilitic		12.6	10.6 in 26 states (Pollock and Furbush) 11.2 in Philadelphia (Strecker and Ebaugh)
Total		100.0	

METHODS OF MEASUREMENT

Hrdlička's anthropologic manual and instruments were used.

The observations could not all be made by one person. At various times we had the aid of M. B. Dodds and S. O. L. Robinson. As each new worker came along, repeated measurements were made until a satisfactory degree of agreement was obtained.

The personal equation as a factor in the precision of measurement will be analyzed numerically in another place.

The metric system was used throughout, weight being determined in kilograms and measurements of length in millimeters.

Dates of birth were recorded and ages calculated to the nearest year, so that 19.5 plus to 20.5 minus was called 20, and so forth; the age group 20 to 30 years—more exactly 19.5 to 29.5—then had a midpoint of 24.5 years.

No clothing was worn, so that all measurements recorded are net.

It was impossible to do all the work at the same hour of the day; in fact, the work went on through a great part of the day. With regard to weight, we are not aware of any tendency to persistent bias through relation to meals

during any part of the series. With reference to stature, which shrinks about a centimeter during about four hours after rising, we assume that our means were affected by the diurnal variation no differently from most measurements, which ordinarily are taken at least an hour after rising and therefore presumably approach the subject's minimum rather than maximum stature.

The season likewise varied.

Choice of Measurements.—On starting an anthropologic project one often wishes to consider the choice of measurements and method made by earlier students of growth and build. The topic was discussed in detail by Gray and Ayres [11] (1931), and head height in particular was further treated in a recent paper on body build in convicts (Gray [8] 1934).

From the point of view of the casual reader, the physician and the mathematically disposed student alike objection may be raised to the mass of data presented in latter day anthropometric studies of build, the objection being to the apparently indiscriminate assembly of measurements substituted for a selection designed to test theories which may be new or old, but unsettled. This objection is based on two points: (1) that a list of all problems meriting solution would be tiresome to the reader, who wants ordinarily, and legitimately, not the hypotheses that stimulated an investigator but such positive (occasionally negative) results as may be achieved, and (2) that one of the problems at issue is the determination of the test traits which may reveal differences with regard to age, race or disease. The tendency has been—to judge by the literature in the physical anthropologic as in other fields—to multiply the items observed in an effort to secure a more nearly complete picture than is yielded by studies of weight and height alone.

STATISTICAL METHODS

The conventional methods which have been specified in earlier papers were used in our compilations. Since much of the computing was done eight years ago, any value after a plus-or-minus sign is to be understood as a probable error, although today this parameter is being more and more commonly abandoned in favor of the standard error (S. E.). Whichever parameter is chosen, it is used to determine the sampling error of the difference between means, a problem continually occurring in medicine and in the past too often judged by guesswork. It is necessary to judge whether a difference which to ordinary inspection appears doubtful is in fact by the experience of probability—that is, according to chance—statistically significant. The judgment is based on the ratio of the difference between the means to the sampling error of that difference. It is customary to consider the difference statistically

11. Gray, H., and Ayres, J. G.: Growth in Private School Children, Chicago, University of Chicago Press, 1931.

significant when the ratio of difference to probable error (P. E.) is 3 or more; or (since P. E.=0.6745 S. E.) when the ratio of difference to standard error is 2 or more. Tables showing the columns necessary in calculation and the successive results for differences, probable error and critical ratio have been shown in previous papers and will be omitted here for the sake of conciseness.

TABLE 2.—*Table of Constants for 180 Schizophrenic White Men Aged 20 to 40 (Mean Age, 31.3)*

Measurement		Mean	± P.E.	S.D.	± P.E.	C.V.	± P.E.
Weight (Kg.)	W	62.800	0.514	10.221	0.363	16.275	0.594
Stature (mm.)	S	1,687.444	3.363	66.888	2.378	3.964	0.141
Sitting height	Si	889.278	1.826	36.332	1.292	4.086	0.146
Chest: Circumference	C	866.222	3.208	63.811	2.268	7.367	0.263
Transverse diameter	T	286.222	1.235	24.566	0.873	8.583	0.307
Anteroposterior depth	AP	213.384	0.922	18.185	0.652	8.522	0.308
Module	ChM	252.904	0.947	18.670	0.669	7.382	0.266
Shoulder (biacromial)	BA	375.472	1.036	20.616	0.733	5.491	0.196
Pelvis (bicristal)	BC	290.278	0.881	17.530	0.623	6.039	0.215
Head: Length	L	191.331	0.386	7.643	0.273	3.994	0.143
Breadth	B	155.107	0.320	6.324	0.226	4.077	0.146
Height	OH	129.698	0.276	5.438	0.195	4.193	0.151
Module	CM	158.638	0.236	4.658	0.167	2.936	0.105
Face: Height	MN	125.788	0.376	7.414	0.266	5.894	0.212
Breadth	BZ	140.602	0.299	5.897	0.211	4.194	0.151
Module	FM	133.268	0.277	5.457	0.196	4.095	0.147
Nose: Height	NH	55.458	0.219	4.319	0.155	7.788	0.281
Breadth	NB	36.045	0.132	2.612	0.094	7.247	0.261
Above named measurements in percentage of stature	W/S	37.189	0.283	5.626	0.200	15.128	0.550
	Si/S	52.767	0.068	1.353	0.048	2.563	0.091
	C/S	51.417	0.204	4.058	0.144	7.892	0.282
	T/S	17.233	0.075	1.498	0.053	8.691	0.311
	AP/S	12.678	0.057	1.133	0.041	8.936	0.323
	ChM/S	15.003	0.058	1.147	0.041	7.643	0.276
	BA/S	22.270	0.063	1.259	0.045	5.655	0.202
	BC/S	17.226	0.047	0.937	0.033	5.437	0.194
	L/S	11.358	0.026	0.521	0.019	4.588	0.164
	B/S	9.220	0.025	0.485	0.017	5.256	0.188
	OH/S	7.696	0.018	0.351	0.013	4.565	0.164
	CM/S	9.423	0.019	0.379	0.014	4.021	0.144
	MN/S	7.462	0.024	0.464	0.017	6.213	0.224
	BZ/S	8.340	0.022	0.439	0.016	5.266	0.189
	FM/S	7.910	0.020	0.389	0.014	4.919	0.177
	NH/S	3.241	0.014	0.280	0.010	8.649	0.312
	NB/S	2.137	0.009	0.175	0.006	8.192	0.296
Index: Chest	AP/T	73.573	0.289	5.709	0.205	7.759	0.280
Trunk breadth	BC/BA	77.622	0.236	4.665	0.166	6.010	0.214
Head	B/L	81.230	0.218	4.316	0.154	5.313	0.190
Face	MN/BZ	89.630	0.275	5.427	0.195	6.055	0.218
Face/head length	MN/L	65.847	0.201	3.971	0.142	6.030	0.217
Face/head breadth	BZ/B	90.672	0.173	3.417	0.122	3.769	0.135
Nose	NB/NH	65.438	0.360	7.093	0.254	10.839	0.393

BASAL CONSTANTS: MEANS AND VARIABILITIES

The original measurements on the patients, the so-called raw data, are omitted because of their bulk. Even the more concise frequency distributions so important to the statistician are omitted. Only the final reduced data are put on record, in three tables of constants (tables 2, 3 and 4), for various age groups. Subsequently the differences will be demonstrated.

TABLE 3.—*Table of Constants for 139 Schizophrenic White Men Aged 40 to 60 (Mean Age, 46.6)*

Measurement		Mean ± P.E.		S.D. ± P.E.		C.V. ± P.E.	
Weight (Kg.)	W	61.755	0.514	8.983	0.363	14.546	0.601
Stature (mm.)	S	1,676.223	3.764	65.793	2.261	3.925	0.159
Sitting height	Si	884.058	1.830	31.866	1.294	3.604	0.147
Chest: Circumference	C	885.432	3.503	61.223	2.477	6.916	0.281
Transverse diameter	T	293.094	1.308	22.855	0.924	7.798	0.317
Anteroposterior depth	AP	224.698	1.067	18.645	0.754	8.297	0.338
Module	ChM	261.194	1.023	17.873	0.723	6.843	0.278
Shoulder (biacromial)	BA	375.489	1.065	18.618	0.753	4.958	0.201
Pelvis (bicristal)	BC	291.281	0.962	16.821	0.680	5.775	0.234
Head: Length	L	191.989	0.392	6.809	0.277	3.547	0.145
Breadth	B	155.113	0.340	5.897	0.240	3.802	0.155
Height	OH	128.182	0.322	5.487	0.228	4.281	0.178
Module	CM	158.394	0.242	4.126	0.171	2.605	0.108
Face: Height	MN	124.821	0.438	7.608	0.310	6.095	0.249
Breadth	BZ	140.147	0.336	5.805	0.237	4.142	0.170
Module	FM	132.779	0.319	5.516	0.226	4.154	0.170
Nose: Height	NH	55.766	0.232	4.028	0.164	7.223	0.296
Breadth	NB	37.015	0.165	2.857	0.116	7.718	0.316
Above named measurements in percentage of stature	W/S	36.820	0.293	5.130	0.208	13.934	0.574
	Si/S	52.703	0.073	1.278	0.052	2.425	0.099
	C/S	52.871	0.227	3.960	0.160	7.490	0.305
	T/S	17.740	0.064	1.473	0.060	8.302	0.338
	AP/S	13.397	0.069	1.198	0.048	8.942	0.365
	ChM/S	15.576	0.065	1.144	0.046	7.343	0.299
	BA/S	22.401	0.067	1.164	0.047	5.197	0.211
	BC/S	17.368	0.053	0.923	0.037	5.312	0.215
	L/S	11.451	0.030	0.523	0.021	4.568	0.187
	B/S	9.273	0.030	0.527	0.021	5.686	0.232
	OH/S	7.653	0.023	0.388	0.016	5.066	0.211
	CM/S	9.451	0.023	0.388	0.016	4.107	0.171
	MN/S	7.459	0.027	0.467	0.019	6.256	0.256
	BZ/S	8.367	0.025	0.431	0.018	5.151	0.211
	FM/S	7.926	0.021	0.369	0.015	4.661	0.191
	NH/S	3.284	0.015	0.254	0.010	7.746	0.318
	NB/S	2.212	0.012	0.201	0.008	9.066	0.372
Index: Chest	AP/T	75.766	0.379	6.623	0.268	8.741	0.356
Trunk breadth	BC/BA	77.665	0.297	5.184	0.210	6.675	0.271
Head	B/L	80.898	0.239	4.153	0.169	5.133	0.210
Face	MN/BZ	89.221	0.329	5.691	0.233	6.379	0.262
Face/head length	MN/L	65.102	0.257	4.461	0.182	6.853	0.281
Face/head breadth	BZ/B	90.456	0.188	3.249	0.133	3.592	0.147
Nose	NB/NH	66.704	0.385	6.681	0.272	10.015	0.412

TABLE 4.—*Table of Constants for 328 Schizophrenic White Men Aged 20 to 80 (Mean Age, 38.9)*

Measurement		Mean ± P.E.		S.D. ± P.E.		C.V. ± P.E.	
Weight (Kg.)	W	62.207	0.360	9.671	0.255	15.547	0.419
Stature (mm.)	S	1,682.317	2.476	66.499	1.751	3.953	0.104
Sitting height	Si	886.575	1.284	34.418	0.908	3.882	0.103
Chest: Circumference	C	874.146	2.354	63.221	1.665	7.232	0.191
Transverse diameter	T	289.177	0.900	24.174	0.637	8.360	0.222
Anteroposterior depth	AP	218.585	0.723	19.328	0.511	8.842	0.236
Module	ChM	256.572	0.699	18.681	0.494	7.281	0.194
Shoulder (biacromial)	BA	375.643	0.730	19.594	0.516	5.216	0.138
Pelvis (bicristal)	BC	290.613	0.652	17.499	0.461	6.022	0.159
Head: Length	L	191.623	0.273	7.286	0.193	3.802	0.101
Breadth	B	155.086	0.230	6.146	0.163	3.963	0.105
Height	OH	128.953	0.208	5.494	0.147	4.261	0.114
Module	CM	158.500	0.167	4.415	0.118	2.786	0.075
Face: Height	MN	125.206	0.273	7.621	0.193	6.087	0.162
Breadth	BZ	140.401	0.219	5.818	0.155	4.144	0.110
Module	FM	132.984	0.207	5.507	0.146	4.141	0.110
Nose: Height	NH	55.663	0.157	4.185	0.111	7.518	0.201
Breadth	NB	36.514	0.104	2.766	0.073	7.574	0.202
Above named measurements in percentage of stature	W/S	36.976	0.203	5.443	0.143	14.719	0.396
	Si/S	52.725	0.049	1.314	0.035	2.492	0.066
	C/S	52.040	0.152	4.082	0.107	7.843	0.208
	T/S	17.459	0.056	1.510	0.040	8.649	0.229
	AP/S	13.013	0.046	1.228	0.032	9.433	0.252
	ChM/S	15.264	0.044	1.186	0.031	7.768	0.207
	BA/S	22.346	0.045	1.212	0.032	5.425	0.143
	BC/S	17.310	0.036	0.970	0.026	5.605	0.148
	L/S	11.401	0.020	0.524	0.014	4.604	0.122
	B/S	9 244	0.019	0.501	0.013	5.420	0.144
	OH/S	7.672	0.014	0.365	0.013	4.764	0.128
	CM/S	9.436	0.014	0.382	0.010	4.044	0.108
	MN/S	7.453	0.018	0.467	0.012	6.261	0.167
	BZ/S	8.354	0.016	0.432	0.011	5.176	0.138
	FM/S	7.914	0.014	0.378	0.010	4.780	0.127
	NH/S	3.265	0.010	0.271	0.007	8.289	0.222
	NB/S	2.173	0.007	0.191	0.005	8.786	0.235
Index: Chest	AP/T	74.623	0.235	6.284	0.166	8.421	0.224
Trunk breadth	BC/BA	77.683	0.187	5.019	0.132	6.460	0.171
Head	B/L	81.077	0.160	4.269	0.113	5.266	0.140
Face	MN/BZ	89.339	0.211	5.602	0.149	6.271	0.167
Face/head length	MN/L	65.437	0.159	4.243	0.113	6.484	0.173
Face/head breadth	BZ/B	90.590	0.125	3.325	0.088	3.670	0.098
Nose	NB/NH	65.986	0.260	6.937	0.184	10.513	0.282

AGE

The effect of increasing age on build must now be examined by noting for each measurement in turn the difference between averages for various age groups in schizophrenia, without distinction of psychiatric type (table 5).

A comparison of the two vicennial subgroups, 20 to 40 and 40 to 60, whose members' ages differ on the average by about fifteen years, showed members of the older group to be statistically smaller only in head height *OH*, perhaps because of baldness. They were larger in size of chest circumference *C*, transverse diameter *T* and anteroposterior depth *AP* and in each of these in relation to stature *C/S*, *T/S* and *AP/S*); in chest index *AP/T*—that is, the depth of the chest increased with age; and in breadth of nose, both absolutely and in relation to stature. The inference results that for comparison of these traits the division used is superior to one into groups covering ranges of more than twenty years. The same could probably have been shown for other traits if we had been more enthusiastic in establishing the thesis and had set up a less conservative criterion.

TABLE 5.—*Relation of Data to Age*

Age Group	Average	Number of Cases
20 to 40	31.3	180
40 to 60	46.4	139
60 to 80	Not calculated	9
20 to 80	38.9	328

Comparing next not subgroup with subgroup but each subgroup with the total, we can lean still further backward, but nevertheless certain differences remain significant statistically.

We compare the total group with the 20 to 40 year group and find the former different—that is, misleading—in that no measurement was too small but the anteroposterior depth *AP* and the module *ChM* of the chest, both of these absolutely and in relation to stature and the ratio of breadth of the nose *NB* to stature were too large.

Comparing similarly the total group with the subgroup from 40 to 60, we find the total significantly in error in that the anteroposterior measurement and the module of the chest were too small, but no measurement was too large.

SUMMARY

Build in schizophrenia is documented by measurements for forty-two items on 328 men in the state of Illinois. The data are reduced to tables of averages and variabilities, not only for the total group but for sub-

divisions according to age. Comparisons of the averages in the light of the error of random sampling show a number of statistically significant changes with age.

The differences in the thoracic measurements support the contention that means for subgroups, even in adult life, are desirable. It must be admitted that thoracic measurements are notoriously uncertain, owing to slight but systematic differences in pressure on the calipers by different observers and to decreased amplitude of breathing on colder days, so that the data for the total group, because of the larger number of cases, may be preferred as more reliable. Apart from the chest, there were significant differences in breadth of the nose and height of the head. Some other measurements showed differences which, though below the level chosen as significant for rigorous fairness, are none the less considerable. Hence, if precise comparisons should be wished, the means for smaller age groups would be useful.

On the whole, the tables of constants for the entire series of 328 subjects, aged 20 to 80 (average 38.9), apparently furnish not only the most comprehensive but the most reliable data for male schizophrenic patients in this country.

This does not take into account the possible difference in build of schizophrenic subjects divided according to clinical types, catatonic, hebephrenic, paranoid and simple. Such comparisons will be presented in another paper.[13]

13. Gray, H.: Body Build and Diagnosis of Schizophrenia, Human Biol., to be published.

CONNECTIONS OF THE PULVINAR

JAMES W. PAPEZ, M.D.

ITHACA, N. Y.

Connections of the pulvinar are still a matter of doubt. For a long time it has been known that lesions of the parietal and occipitotemporal regions may give rise to degeneration of fibers in the pulvinar. Dejerine [1] reported a number of such cases: those described by Courrière, Bras, Jouan, Leudot, Seguillon, Rivaud and others. In these cases a clinical history was available. The extent of the cortical lesions was calculated in each case, and a well illustrated histologic analysis, showing how the pulvinar was affected, was given.

The case reported here is one of several which illustrate connections between the occipitotemporal and parietal association areas and the pulvinar. The brains in a number of other cases have been sectioned and studied. They will be reported on later. Some general inferences are drawn from these cases and from other sources.

REPORT OF A CASE

History.—J. C., a woman aged 23, was admitted to a state hospital in 1882, with a diagnosis of dementia praecox of the hebephrenic variety. The case was such that no anamnesis was obtainable. There was definite loss of mental functions. The patient was unable to comprehend or converse. She was quiet, silent, smiling and silly. She was always indifferent to her surroundings, but at times was inclined to collect rubbish. She was idle and occasionally destructive. The motor functions and physical condition were good. Her condition persisted with little change for more than fifty years, during which she remained in the institution. Toward the end she showed gradual deterioration and senile physical changes.

In 1932 she suffered a fracture of the left radius, from which she made a good recovery. On Sept. 14, 1936, she suffered a simple fracture of the neck of the femur. This was treated with traction. Her physical condition was then extremely poor. On September 22 the temperature was 102 F., the respiratory rate 24 and the pulse rate 60. She was incontinent. The following day the temperature, pulse and respiration were normal. Later, it was noted that the muscles of the neck were somewhat rigid. Slight bilateral twitchings of the muscles of the shoulders, arms and hands were observed. She was unable to swallow. She died on September 25 at the age of 77. The contributing cause of death was given as general arteriosclerosis.

Autopsy.—The brain was removed early on the following day and fixed in a neutral solution of formaldehyde. The cerebral vessels were moderately sclerotic. There was a large cavity in the cortex of the right temporal lobe

From the Department of Anatomy, Cornell University.

1. Dejerine, J.: Anatomie des centres nerveux, Paris, J. Rueff, 1901.

which had the appearance of a softening of long standing, possibly due to an abscess of the temporal lobe or thrombosis of the temporal branches of the middle cerebral artery (fig. 1). The inferior frontal, the ascending frontal and the ascending parietal branches of this artery were not involved. The artery to the supramarginal gyrus and the temporal branches were lost in the region of the softening. The left hemisphere was nearly normal in appearance. The unaffected parts of the right hemisphere had a good vascular supply, but showed considerable atrophy, which was especially evident in the posterior parietal region, where the lateral ventricle was much distended, and in the right frontal polar cortex.

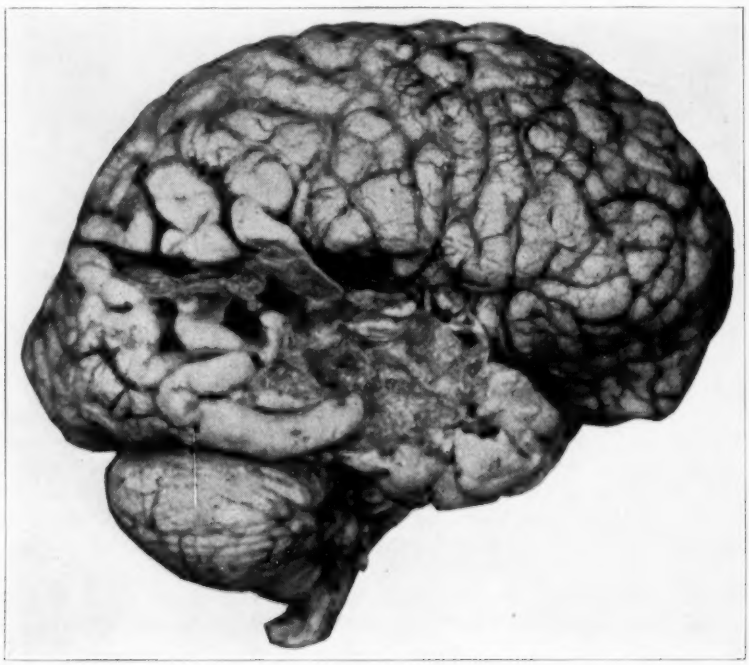

Fig. 1.—Lateral view of the right hemisphere, showing extent of the cortical lesion in the temporal and lower parietal regions.

The extent of loss of cortical tissue is illustrated in figure 1. The cavity extended into the ventricle. The lesion spared the lower part of the temporal region.

The acoustic radiations to the superior temporal cortex, the local association bundles, the superior longitudinal fasciculus and the connections of the posterior parietal, temporal, parieto-occipital and temporo-occipital cortical areas were completely disconnected from the thalamus. Only the lower band of the optic radiation passing through the inferior temporal region remained intact. As a result of the lesion, the lateral geniculate body, the medial geniculate body and the pulvinar were nearly devoid of cortical connections. These thalamic nuclei were grossly reduced. The pulvinar and its forward extension, the nucleus lateralis anterior, were severly atrophied. The geniculate bodies were partially preserved.

The brain stem was removed (fig. 2), mordanted in potassium bichromate and embedded in pyroxylin. It was sectioned at 40 microns. Every tenth section was stained, by Mr. W. Rundles, by a modification of the Weigert-Pal method for fibers, and a corresponding section was stained for cells with cresyl violet. The right occipital lobe was sectioned serially and stained.

Examination of the brain case showed a small, spongy dural tumor, about the size of a split bean, situated on the right side under the tentorium on the posterior surface of the petrous part of the temporal bone. Its position was just lateral and dorsal to the internal acoustic meatus. It was tightly adherent to the petrous bone and to a fibrous thickening around the medial end of the superior petrosal (venous) sinus.

Histologic Changes.—Serial sections included the corpus striatum, thalamus, midbrain, pons and right occipital lobe. In general, the left half of the brain stem was normal, showing well developed structures. Structural deficiencies appeared on the right side. The most notable was the absence of the pulvinar.

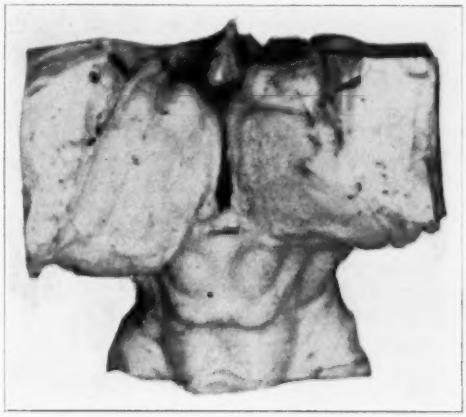

Fig. 2.—Dorsal view of the upper part of the brain stem, showing total absence of the pulvinar and nucleus lateralis anterior on the right side.

There was severe reduction of the lateral portion of the medial nucleus. The medial and lateral geniculate bodies were reduced to rudiments. The anterior commissure was severely degenerated bilaterally (fig. 4 *B*, *ca*).

The afferent pathways in general were well developed. The medial lemniscus and the spinothalamic tract were large and normal on both sides (fig. 3 *A* and *B*, *ml*, *st*). They ended in the usual way in the ventral lateral nucleus (pars externa) of the thalamus (fig. 4 *A* and *B*, *vl*). On the right side this nucleus was somewhat reduced, but it had well preserved connections through the internal capsule with the sensorimotor area of the cortex. At the caudal level of the thalamus the medial lemniscus and the spinothalamic tract came into relation with the anterior tegmental nucleus (fig. 3 *A* and *B*, *at*). Meynert's decussation (*d*) arose from this nucleus, followed the optic tract and ended in the hypothalamus. This decussation appeared normal on both sides. This condition agrees with that seen in a hemidecorticate dog.[2] It indicates that Meynert's decussation connects the proprioceptive and cutaneous pathways with the hypothalamus.

2. Papez, J. W.: Thalamic Connections in a Hemidecorticate Dog, J. Comp. Neurol. **69**:103-120, 1938.

EXPLANATION OF FIGURE 3

Fig. 3.—*A*, cross section of the midbrain through the level of the optic tectum and the middle of the red nuclei. Note the normal size of the geniculate bodies (*lg*, *mg*) and the pulvinar (*pi*, *pl* and *pd*) on the left and their total absence on the right. Note, also, the demyelination of the right tectum (*tec*).

B, cross section of the thalamus through the level of the posterior commissure (*cp*). Note the remnants of the geniculate bodies on the right (*mg*, *lg*) and the total atrophy of the pulvinar (*pul*). Weigert stain; × 1¼.

In this figure and in figure 4, the following abbreviations are used: *al* indicates the ansa lenticularis; *arc*, the arcuate nucleus; *at*, the anterior tegmental nucleus; *b*, the temporothalamic fasciculus; *bc*, the brachium conjunctivum; *bic*, the brachium of the inferior colliculus; *c*, the thalamic commissure; *ca*, the anterior commissure; *cm*, the central median nucleus; *cp*, the posterior commissure; *ct*, corticotectal fibers; *d*, the ventral supraoptic decussation; *dd*, the dorsal supraoptic decussation; *f*, the fornix; *fl*, the fasciculus lenticularis; *int*, the internal capsule; *la*, the nucleus lateralis anterior; *lg*, the lateral geniculate body; *m*, the medial nucleus of the thalamus; *mb*, the mamillary body; *md*, the lateral part of the medial nucleus; *mg*, the medial geniculate body; *ml*, the medial lemniscus; *mt*, the mamillothalamic tract; *nr*, the red nucleus; *oc*, the oculomotor nerve; *on*, the oculomotor nucleus; *or*, the optic radiation; *ot*, the optic tract; *p*, the pallidum; *pd*, the dorsal portion of the pulvinar; *ped*, the basis pedunculi; *pi*, the inferior portion of the pulvinar; *pl*, the lateral portion of the pulvinar; *pp*, the parietopontile tract; *pr*, the pallidoreticular tract; *ps*, the pallidosubthalamic tract; *pv*, periventricular fibers; *pul*, the pulvinar; *put*, the putamen; *r*, the reticular nucleus; *rp*, radiations of the pulvinar; *s*, strionigric fibers; *sn*, the substantia nigra; *st*, the spinobulbothalamic tract; *ste*, the subthalamicotegmental tract; *su*, the subthalamic nucleus; *t*, the dorsal trigeminal tract; *ta*, the amygdalar tract; *tec*, the optic tectum; *v*, the pars ventralis of the geniculate bodies; *vi*, the ventral intermediate nucelus; *vl*, the ventral lateral nucleus, and *vm*, the ventral medial nucleus.

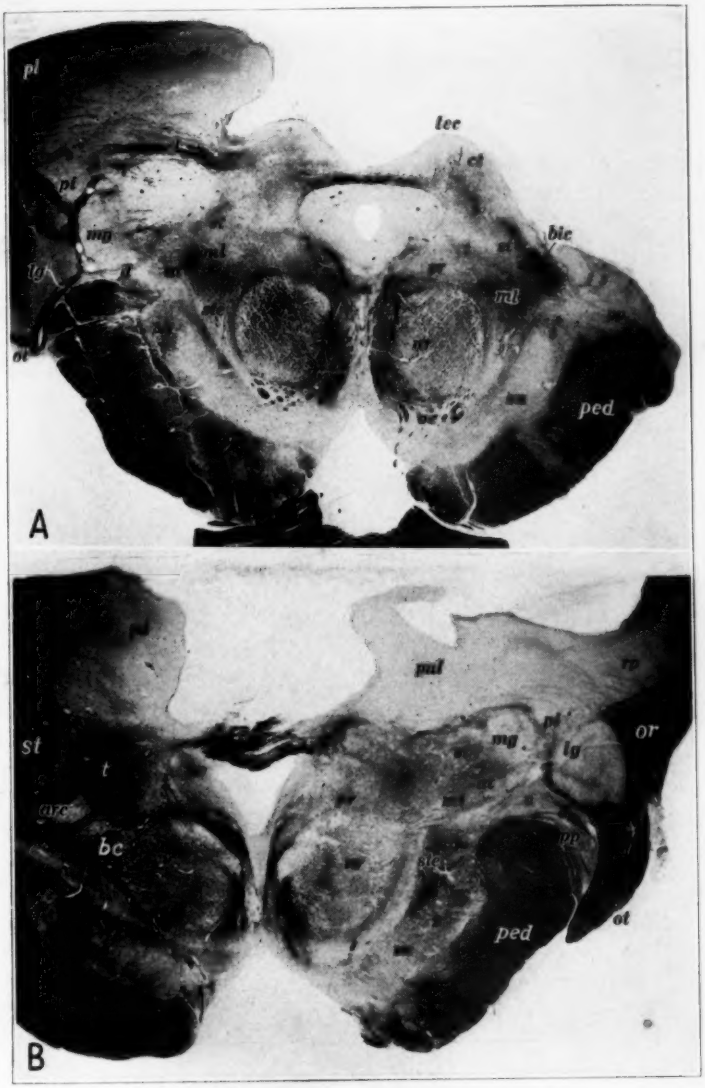

Figure 3

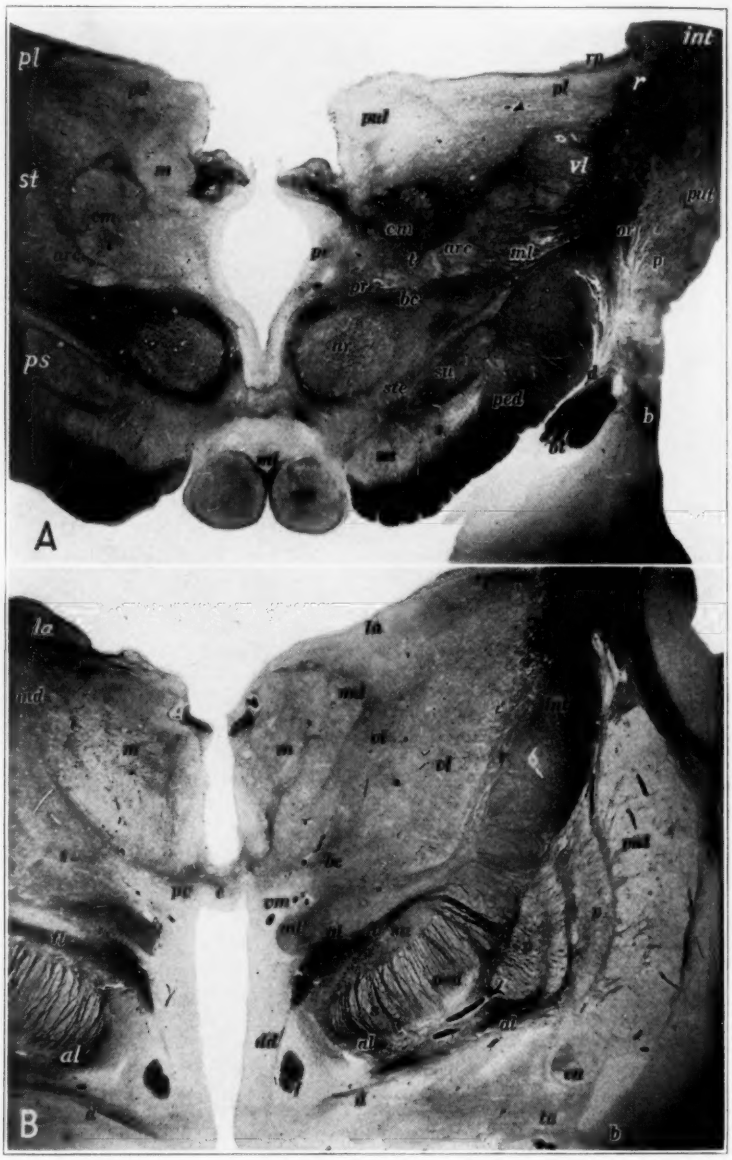

Fig. 4.—*A*, cross section of the thalamus through the level of the central median nucleus (*cm*) and the mamillary body (*mb*). Note the atrophy of the pulvinar on the right (*pul*).

B, cross section of the corpora striata and the anterior half of the thalamus, in front of the optic chiasm. Note the normal nucleus lateralis anterior on the left (*la*) and its absence on the right. The medial nucleus on the right (*m*) is reduced. Weigert stain; × 1¼.

The lateral lemniscus (acoustic pathway) was normal up to the inferior colliculus. Above this, the brachium of the inferior colliculus was reduced in size (fig. 3 *A, bic*) and ended in a rudimentary medial geniculate body (fig. 3 *B, mg*). The amount of reduction was evident when compared with the normal left geniculate body (fig. 3 *A, mg*). Acoustic radiations to the cortex were absent on the right side.[3] The preservation of some of the cells in the right medial geniculate body is comparable with that seen in the monkey after complete temporal lobectomy [4] and in a hemidecorticate dog.[2] The supraoptic decussation of Gudden (fasciculus arcuatus corporis geniculati lateralis) was normal on both sides. It appeared to arise from the well defined pars ventralis, which lies ventral to the medial geniculate body and medial to the lateral geniculate body (fig. 3 *B, v*). This, again, is in conformity with the relations observed in the dog, namely, that the pars ventralis and Gudden's decussation connect the optic and acoustic systems with the hypothalamus.[2]

The optic tract was slightly smaller on the right side. It ended in a much reduced lateral geniculate body (fig. 3 *B, lg*). The amount of shrinkage was evident when compared with the normal lateral geniculate on the left side (fig. 3 *A, lg*). The lower horizontal band of the optic radiation to the area striata (visual area) of the occipital pole was preserved (fig. 3 *B, or*). This arose from the lateral horn of the lateral geniculate body, the cells of which were present. It passed to the occipital cortex through the inferior temporal region.

In sections of the occipital pole, the vertical and the superior horizontal band of the optic radiation were represented by a sclerotic zone. A part of the inferior horizontal band which traversed the inferior temporal region was present, representing about 20 per cent of the total radiation. The area striata (visual area) was well preserved and definitely delimited by a prominent stria or line of Gennari and by a normal stratum calcarinum on the ventricular surface. The line of Gennari, or Vicq d'Azyr, was clearly not formed by terminals of the optic radiation, as is commonly stated. In this case, at least 80 per cent of the optic radiation was totally atrophied. The striate cortex of the cuneus supplied by the atrophic radiation contained a line of Gennari as distinct as that in the cortex of the lingual gyrus, supplied in part by normal fibers. The deficiency in neuropil was more definite in the deeper layer IVc (Rundles and Papez [4]).

There was definite demyelination of the right optic tectum, due to loss of the corticotectal fibers (fig. 3 *A, ct*). This commonly occurs with lesions of the posterior parietal cortex.[1]

The central tegmental fasciculus was normal on the left side, but somewhat diminished on the right. The dorsal trigeminal tract, which ascended in this bundle, was slightly smaller on the right (figs. 3 *B* and 4 *A, t*). The central median nucleus (*cm*) and the arcuate nucleus of the thalamus (*arc*), in which the dorsal trigeminal tract ended, were both slightly reduced.[5] The arcuate nucleus had thalamocortical connections through the internal capsule, probably

3. Walker, A. E.: The Projection of the Medial Geniculate Body to the Cerebral Cortex in the Macaque Monkey, J. Anat. **71**:319-331, 1937.

4. Rundles, R. W., and Papez, J. W.: Fiber and Cellular Degeneration Following Temporal Lobectomy in the Monkey, J. Comp. Neurol. **68**:267-296, 1938.

5. Papez, J. W., and Rundles, R. W.: The Dorsal Trigeminal Tract and the Centre Median Nucleus of Luys, J. Nerv. & Ment. Dis. **85**:505-519, 1937.

to the lower part of the central gyri.[6] There is direct evidence that the cortex of these gyri is concerned with afferent impulses from the tongue, mouth and lips.[7]

The outstanding feature of this case was the loss of the pulvinar on the right side. The radiations of the pulvinar which connect the parietal and parieto-occipital cortex with the pulvinar[8] were completely cut off and removed by the cortical lesion (fig. 3 *B*, *rp*). Also, the association fibers which normally ascend from the temporal cortex to the posterior parietal and the occipital cortex were absent.

The pulvinar on the right side was totally degenerated except for a strip of fibers and cells in its oral portion (figs. 3 *B* and 4 *A*, *pul*). Its narrow forward extension over the dorsal surface of the thalamus, the nucleus lateralis anterior or dorsal disseminate nucleus, was also absent (fig. 4 *B*, *la*). The pulvinar was observed to be more normal on the left side (fig. 4 *A* and *B*). It may be divided into three portions: the inferior pulvinar (*pi*, intergeniculate body, or *Hinterkern*); the lateral pulvinar (*pl*); the dorsal pulvinar (*pd*), and the oral continuation of the pulvinar, called the nucleus lateralis anterior (*la*), or dorsal disseminate nucleus. The fiber connections, neuropil and cells of these parts were largely absent on the right side. The more anterior part of the pulvinar retained a strip of fibers (fig. 4 *A* and *B*, *rp*) associated with a strip of cells. These fibers appeared to come from fiber bundles which were connected with the postcentral cortex. Connections between the pulvinar and the medial nucleus were grossly affected.

In the normal thalamus, numerous fiber connections are seen extending forward and medially from the pulvinar into the medial nucleus. The lateral border of the medial nucleus normally exhibits masses of large cells and wreaths of neuropil. Great development of this area is characteristic of the human thalamus. The loss of this feature was seen on the right side (fig. 4 *B*, *md*). Even the connections of the nucleus lateralis anterior (*la*), or dorsal disseminate nucleus, were lost.

The medial nucleus of the thalamus was reduced in size as well as in fiber content (fig. 4, *m*). This reduction affected chiefly its lateral aspect (fig. 4 *B*, *md.*). Sections stained with cresyl violet showed apparent reduction in the anterior thalamic radiation on the right side, which was probably associated with the reduction of the lateral part of the medial nucleus.

The medial portion of the medial nucleus remained intact, and its connections with the corpus striatum by way of the inferior thalamic peduncle appeared normal.

The large bundle normally connecting the amygdala and piriform cortex (uncinate gyrus) with the pulvinar was severed and degenerated by the lesion on the right. This temporothalamic fasciculus, or bundle of Arnold, deserves mention. Dejerine[9] demonstrated its origin from the tip of the temporal lobe and its termination in the pulvinar. Rundles and I[4] showed that in the monkey it has similar connections. I[10] described this bundle in Pithecus (Macacus) rhesus and noted its constancy in various series of human brains. In man it is con-

6. Clark, W. E. L.: The Connections of the Arcuate Nucleus of the Thalamus, Proc. Roy. Soc., London, s.B **123**:166-176, 1937.

7. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**: 389-443, 1937.

8. Clark, W. E. L., and Northfield, D. W. C.: The Cortical Projection of the Pulvinar in the Macaque Monkey, Brain **60**:126-142, 1937.

9. Dejerine,[1] p. 42.

10. Papez, J. W.: Reciprocal Connections of the Striatum and Pallidum in the Brain of Pithecus (Macacus) Rhesus, J. Comp. Neurol. **69**:329-349, 1938.

siderably enlarged, the magnitude of the cross section being somewhat greater than that of the optic tract. The bundle arises from the fiber stratum between the piriform cortex and the amygdala and passes back under the internal capsule, in close relation to the terminal stria and the tail of the caudate nucleus. It shifts medially across these structures. It comes to occupy a position lateral to the lateral geniculate body and ventral to the optic radiation. It curves around the posterior border of the internal capsule and passes upward to join the radiations of the pulvinar, in which it terminates.

The lesion in this case extended across a number of structures lateral to the pulvinar, all of which were degenerated. Among these were the terminal stria, the caudal end of the pallidum, the tail of the caudate nucleus and the strionigric fibers from the tail of the caudate nucleus.

The caudal end of the pallidum and the tail of the caudate nucleus were destroyed by the lesion on the right side (fig. 3 *B*). Except for this, the corpus striatum was practically normal on both sides (fig. 4 *B*, *p*, *put*). The pallidum gave origin to the usual tracts (*fl*, *al*), which passed to the red nucleus and to the subthalamic nucleus (fig. 4 *A*, *su*). The putamen and head of the caudate nucleus gave origin to the striopallidal fibers and to the strionigric fibers seen in the basis pedunculi (figs. 3 and 4, *s*). Only the tail of the caudate nucleus was absent on the right side. Associated with this was atrophy of the strionigric fibers from the tail of the caudate nucleus to the lateral and caudal parts of the substantia nigra (fig. 3 *A*, *s*). These fibers normally pass, like spokes of a wheel, through the posterior part of the internal capsule, which in this case was almost totally degenerated on the right side.[10] The absence of these strionigric fibers accounted for the reduction of the lateral and caudal parts of the substantia nigra on the right. Aside from this, the substantia nigra and its fiber connections on both sides were well preserved.

The red nuclei and the rubrospinal tracts were normal. There was definite loss of fibers in the field dorsal to the red nucleus (fig. 3 *A*, *pr*) on the right, due probably to injury to the caudal end of the pallidum. The subthalamicotegmental tracts were normal (figs. 3 and 4 *A*, *ste*). The tegmental connections of the substantia nigra and the descending tegmental bundles were well preserved, though somewhat reduced on the right side.

The parietopontile tract was severely atrophic, as seen in the lateral border of the right basis pedunculi (fig. 3 *A* and *B*, *pp*). The basis pedunculi was reduced in volume by 25 per cent, largely owing to loss of this tract. The cortical lesion (fig. 1) extended deeply to the ventricle, severing completely the posterior parietal contingents of this tract. From experimental evidence presented in another paper,[4] it seems that this extrapyramidal tract to the pons and cerebellum comes from the parietal region. The origin of these extrapyramidal fibers is probably the posterior parietal extent of the extrapyramidal areas indicated by Penfield and Gage[11] and Foerster.[12]

COMMENT

The lesion in this case destroyed a large part of the right temporal lobe and its immediate fiber connections. The acoustic radiation was absent. Most of the small cells of the medial geniculate body were lost. Some of the large cells on the medial side were spared. The pars ven-

11. Penfield, W., and Gage, L.: Cerebral Localization of Epileptic Manifestations, A. Research Nerv. & Ment. Dis., Proc. **13**:593-613, 1934.

12. Foerster, O.: The Motor Cortex in Man in the Light of Hughlings Jackson's Doctrines, Brain **59**:135-159, 1936.

tralis of the medial and the lateral geniculate body was not affected. The inference is that not all cells of the medial geniculate body have cortical connections. Connections of the remaining cells and of the pars ventralis may be of two orders: fibers which form the supraoptic decussation of Gudden passing to the hypothalamus and fibers which pass to the corpus striatum.[2]

The suprageniculate nucleus was almost totally absent. The nucleus limitans was well preserved, which again demonstrates its independence of the temporal cortex.

The connection of the lateral geniculate body with the area striata of the occipital pole is well known.[13] The deep temporal lesion interrupted most of the optic radiation, except the fibers of the inferior horizontal band which passed through the inferior part of the temporal lobe.

There was a corresponding loss of cells in all but the lateral horn of the lateral geniculate body. This was readily verified, since the remaining cells of the two magnocellular laminas were seen on the medial side.

The removal of the optic radiation did not in any way cause degeneration of the stria or line of Gennari. It has been shown that the optic radiation ends mainly in layer IVc and not in the stria of Gennari.[4] The origin of the stria depends on the intactness of the stratum calcarinum. A lesion in any part of the area striata causes degeneration of fibers to all other parts of this area.[14] These fibers pass through the stratum calcarinum.

The obvious inference is that the stratum calcarinum is a local association layer which enters and leaves the striate cortex and forms the stria of Gennari. Although there is a point for point projection from the retina on the area striata, it is obvious that the primary visual pattern must be a total one, spread over the entire area striata. This has an important functional implication, for whatever the contour of the stimulus pattern emblazoned on the area striata, the result should be a total reaction within the whole area striata, irrespective of the spatial relations or orientation of the stimulus object.[15] The further spread of such excitation into the parastriate and peristriate areas and beyond into the parietal cortex should result in a wide field of excitation underlying the functions of perception.

---

13. Poliak, S.: The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Berkeley, Calif., University of California Press, 1932.

14. Mettler, F. A.: Corticifugal Fiber Connections of the Cortex of Macaca Mulatta: The Occipital Region, J. Comp. Neurol. **61**:221-256, 1935.

15. Bender, L.: Gestalt Function in Visual Motor Patterns in Organic Disease of the Brain, Arch. Neurol. & Psychiat. **33**:300-328 (Feb.) 1935.

The outstanding feature of this case was total loss of the pulvinar. The pulvinar receives its afferent connections mainly from the posterior parietal and adjacent cortex.[16] It is not related to any specific sensory pathway passing to the cortex, as is often supposed.[8] In this respect it differs from most other thalamic nuclei, which serve primarily as relays in some afferent pathway for stimuli from bodily sources.[17]

It is probable that the temporal cortex does not project directly on the pulvinar, with the possible exception of the inferior portion of the pulvinar.[4] The temporal cortex is, however, strongly connected with the parietal and occipitotemporal cortex. The radiations of the pulvinar coming from the occipitoparietal and occipitotemporal cortex converge on the optic radiation, which they accompany. They form a large part of the retrolenticular part of the internal capsule. In the side of the pulvinar they appear as a conspicuous zone of fibers above the optic radiation. This zone of fibers streams inward through the lateral portion of the pulvinar. A small band of corticotectal fibers enters the optic tectum. The cells of the pulvinar project fibers back to the same cortex. Thus, a two way connection appears to exist between the posterior association cortex and the pulvinar. The pulvinar receives also the temporothalamic fasciculus of Arnold from the piriform cortex and amygdala.[18] This is a one way connection, which probably conducts visceral experiences (uncinate functions) to the pulvinar.

Transthalamic connections between the pulvinar and the medial nucleus appear to be abundant. Whether they arise as short fibers from the cells of the pulvinar or represent terminals of cortical cells is a question. The presence of these transthalamic fibers offers an explanation of the innervation of the medial nucleus, especially its lateral large-celled portion.[19] It is a question whether the nucleus centralis lateralis should be included in this complex.[20] The lateral portion of the medial nucleus consists of large cells which send the large anterior thalamic radiation to the frontal polar cortex.[19] This also is a two way connection. In the present case it was considerably reduced.

The observation in this and in 2 other cases suggests the existence of an extensive transthalamic connection between the posterior association areas and the frontal cortex, and back again. These transthalamic

16. Dejerine.[1] Rundles and Papez.[4] Clark and Northfield.[8]

17. Papez, J. W.: The Brain Considered as an Organ: Neural Systems and Central Levels of Organization, Am. J. Psychol. **49**:217-232, 1937.

18. Dejerine.[1] Rundles and Papez.[4] Papez.[10]

19. Walker, A. E.: The Thalamus in Relation to the Cereberal Cortex, J. Nerv. & Ment. Dis. **85**:249-261, 1937.

20. Papez, J. W., and Aronson, L. R.: Thalamic Nuclei of Pithecus (Macacus) Rhesus: I. Ventral Thalamus, Arch. Neurol. & Psychiat. **32**:1-26 (July) 1934. Aronson, L. R., and Papez, J. W.: Thalamic Nuclei of Pithecus (Macacus) Rhesus: II. Dorsal Thalamus, ibid. **32**:27-44 (July) 1934.

connections are mediated by fibers passing between the pulvinar and the lateral portion of the medial nucleus. This system of connections is schematically represented in figure 5. The connections, however, are in both directions.

In the case of J. C. there was complete aphasia with severe amentia, probably due to the organic lesion. The functions of perception were markedly reduced, and those concerned with thinking were largely absent. The motor functions were not obviously impaired. The absence of epilepsy is noteworthy.

The brains in 2 other cases have been studied, but are not reported on here. One patient, who clinically presented global aphasia and

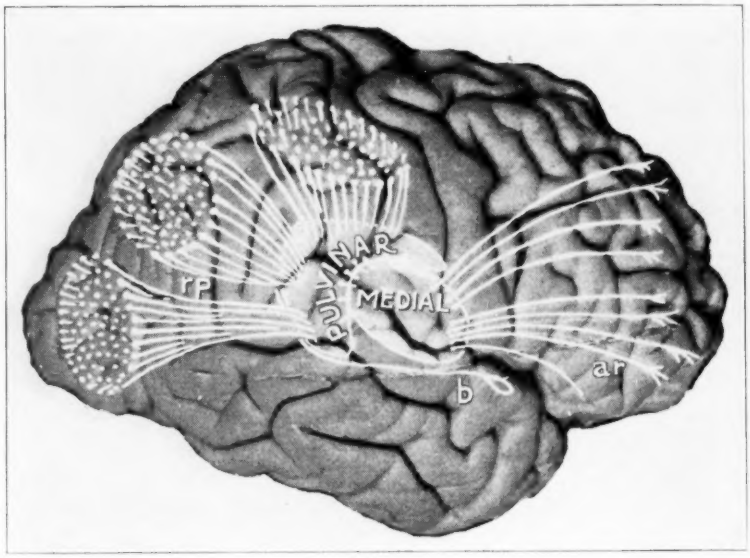

Fig. 5.—Diagram showing the transthalamic connections of the posterior association areas through the pulvinar and the medial nucleus with the frontal pole. Note the bundle (*b*) from the amygdala to the pulvinar.

amentia, had a large temporoparietal softening on the left side, which involved loss of the pulvinar and other thalamic nuclei. The other patient, who clinically presented aphasia and a psychosis, had a traumatic softening of the postsylvian cortex associated with demyelination of the tectum and of the pulvinar and loss of some cells of the pulvinar. From numerous verified cases of aphasia [21] it seems that the functions of perception are seriously affected by diseases of the temporal, occipital

21. Henschen, S. E.: Ueber Aphasie, Amusie und Akalkulie, in Klinische und anatomische Beiträge zur Pathologie des Gehirns, Leipzig, Breitkopf & Hartel, 1920, pt. 5.

and parietal association areas. When, in addition, the pulvinar and its connections are involved more serious mental disorders and deficiencies occur. It is possible that the transthalamic connections of the posterior association areas with the frontal polar cortex may represent a special cerebral mechanism dealing with comprehending and elaborative thinking.[22]

SUMMARY

A case of long-standing aphasia and dementia is reported in which the right temporal lobe had been largely destroyed. The medial and lateral geniculate bodies were reduced on the same side, in correspondence with loss of the acoustic and optic radiations. The right tectum opticum was partly demyelinated. A large part of the parietopontile tract was degenerated. The oustanding defect was total absence of the right pulvinar, absence of fibers between the pulvinar and the medial nucleus and atrophy of the lateral large-celled part of the medial nucleus of the thalamus. This case and 2 similar cases suggest that there is an extensive transthalamic connection between the posterior association cortex and the frontal polar cortex through the medium of the pulvinar and the medial nucleus.

22. Papez, J. W.: Cerebral Mechanisms, J. Nerv. & Ment. Dis., to be published.

SYNCOPE, CONVULSIONS AND THE UNCONSCIOUS STATE

RELATION TO THE HYPERACTIVE CAROTID SINUS REFLEX

LEON J. ROBINSON, M.D.
PALMER, MASS.

The occurrence of syncope and convulsions due to a hyperactive carotid sinus reflex has been receiving deserved emphasis lately.[1] The carotid sinus is the bulbous dilatation at the bifurcation of the common carotid artery. Normally an increase in intrasinal pressure reflexly produces a moderate decrease in arterial tension, cardiac rate and output of epinephrine, while respiration and peristalsis are increased. In a patient with a hypersensitive carotid sinus, stimulation of the sinus by pressure will often induce syncope or convulsions as well as other manifestations.

The three dominant sinal responses are: (1) the vagal type, with the efferent impulse traveling over the vagus nerve to produce sinoauricular or auriculoventricular block, with resultant asystole and syncope; (2) the depressor type, the efferent arc of which over the aortic depressor nerves accounts for vasodilatation and hypotension unassociated with bradycardia, and (3) the cerebral type, in which syncope occurs without cardiovascular changes. The vagal type of sinal syncope can be prevented by administration of atropine (which inhibits the vagus nerve) or of epinephrine (which stimulates the cardiac

---

From the Monson State Hospital.

Read at a meeting of the Boston Society of Psychiatry and Neurology, Oct. 21, 1937.

1. (*a*) Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Role in the Causation of Fainting and Convulsions, Medicine **12**:297-354 (Sept.) 1933. (*b*) Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions: A Study of Thirty-Two Additional Cases, ibid. **14**:377-456 (Dec.) 1935. (*c*) Weiss, S.; Capps, R. B.; Ferris, E. B., Jr., and Munro, D.: Syncope and Convulsions Due to a Hyperactive Carotid Sinus Reflex, Arch. Int. Med. **58**: 407-417 (Sept.) 1936. (*d*) Smith, H. L., and Moersch, F. P.: Syncope of Patients with Hypersensitive Carotid Reflexes, Proc. Staff Meet., Mayo Clin. **10**:401-406 (June 26) 1935; (*e*) Further Study on the Hypersensitive Carotid Sinus Reflex Syndrome, ibid. **11**:380-384 (June 10) 1936. (*f*) Roskam, J.: Un syndrome nouveau: Syncopes cardiaques graves et syncopes répetées par hyper-réflectivité sinocarotidienne, Presse méd. **38**:590-591 (April 30) 1930. (*g*) Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation: An Anatomical, Experimental and Clinical Investigation, Acta psychiat. et neurol. (supp.) **6**:1-348, 1935.

muscle directly). The depressor type of attack is abolished by epinephrine (which prevents vasodilatation). Anesthesia of the carotid sinus induced by procaine hydrochloride or surgical denervation of the carotid sinus abolishes an abnormal response of any of the three types.

Previous reports of cases of the carotid sinus syndrome in a general hospital clinic have failed to state the number of persons tested; hence the percentage incidence in the populace so tested is unknown.[1]

Forty-seven cases were reported by Weiss and his colleagues (Weiss and Baker;[1a] Ferris, Capps and Weiss;[1b] Weiss, Capps, Ferris and Munro[1c]). Smith and Moersch[1d, e] reported 35 cases, Roskam[1f] and Missal and Crain[2] reported 2 cases, and Ask-Upmark[1g] apparently observed many cases. In his study of the carotid sinus reflex Sigler[3] reported slowing of the cardiac rate in many patients but made no mention of syncope. Lennox (personal communication to Weiss[1a]) did not find a single instance of an abnormal carotid sinus in 150 epileptic patients.

With these facts in mind, this study was undertaken to determine the incidence of the hypersensitive carotid sinus reflex among 1,000 patients with epilepsy. The subjects included cooperative institutional patients in the wards as well as outpatients at the Monson State Hospital, an institution for the care of epileptic patients in Massachusetts.

MATERIAL AND METHOD

In every instance syncope, convulsions or transitory loss of consciousness had brought the patient to the hospital. Among the ward patients exhibiting a hyperactive carotid sinus mechanism, institutionalization was indicated for adequate causes (aside from syncope), such as mental deficiency, mania or periods of dementia.

With the patient standing, firm digital pressure was exerted over that part of the carotid artery felt pulsating in the neck from the cricoid cartilage to the angle of the jaw. Pressure was maintained for one minute. To prevent fatal cardiac stoppage, only one side was stimulated at a time. Before the test the patient was reassured. The blood pressure and the pulse rate were determined at this time as well as during maintenance of pressure on the carotid sinus.

INCIDENCE OF CAROTID SINUS SYNDROME

Of the 1,000 patients in this series, 9 had a hyperirritable carotid sinus reflex. The incidence of the carotid sinus syndrome in the group tested was therefore 0.9 per cent. A tabulation of the results is presented. Four patients (cases 1, 2, 3 and 7) presented a vagal and depressor

2. Missal, M. E., and Crain, R. B.: Alternation Phenomena in the Electrocardiogram: Occurrence in a Patient with Active Carotid Sinus Reflex, Am. Heart J. **11**:611-618 (May) 1936.

3. Sigler, L. H.: Clinical Observations on the Carotid Sinus Reflex, Am. J. M. Sc. **186**:118-125 (July) 1933.

response; 3 patients (cases 4, 5 and 6), a vagal, depressor and cerebral response, and 2 patients (cases 8 and 9), a purely cerebral response.

A hyperirritable carotid sinus reflex seemed to be the sole mechanism underlying all seizures, spontaneous and induced, in 5 cases (cases 1, 2, 3, 6 and 7). Three patients exhibited a hypersensitive carotid sinus reflex and also were known to have an additional convulsive mechanism (cases 4 and 8, the patients having epilepsy of unknown cause; case 5 the patient having symptomatic epilepsy). The ninth patient died of an intercurrent illness before sufficient studies could be performed for accurate analysis. It was obvious that he had a hyperirritable carotid sinus reflex and probably an additional convulsive mechanism.

Age.—The ages of the 1,000 patients tested for the presence of the syndrome ranged from 4 to 82 years. The nine patients with the hyperirritable sinus syndrome ranged in age and sex as follows: 1 boy aged 14; 1 girl aged 19; 1 man aged 24; 2 men aged 57; 1 man aged 69; 1 man aged 70; 1 man aged 71, and 1 man aged 79. The fact that no instance of hyperirritable sinus was discovered in any patient under 14 years of age seems to be merely accidental.

Hyperirritable Carotid Sinus Reflex

Case	Type of Hyperirritable Carotid Sinus Response			Additional Convulsive Mechanism
	Vagal	Depressor	Cerebral	
1	+	+	0	0
2	+	+	0	0
3	+	+	0	0
4	+	+	+	+
5	+	+	+	+
6	+	+	+	0
7	+	+	0	0
8	0	0	+	+
9	0	0	+	?

In agreement with others,[1a] I found that the incidence of dyspnea, hyperpnea or vertigo (unaccompanied by syncope and seen in many patients purposely excluded from this report) paralleled the degree of arteriosclerosis and therefore the age of the patient. However, the readiness with which syncope could be induced was less dependent on these factors.

Sex.—Since a larger number of male than female patients were examined, the apparently greater incidence of hyperirritable sinus reflex among males is not as significant as might be supposed. However, one observer noted a ratio of 33 males to 2 females in a series of 35 clinic cases of abnormal sinus reflex.[1e]

It has been demonstrated by Weiss and his colleagues[1c] that both the vagal and the depressor type of hyperirritable sinus response can be prevented by administration of epinephrine or ephedrine. In 5 of my cases in which depressor effects were evident, epinephrine was effective

in preventing induction of syncope by pressure over the carotid sinus (cases 1, 2, 3, 4 and 7). The disadvantage of epinephrine for continuous use is the necessity of hypodermic injection. Therefore, as suggested by Weiss,[1c] ephedrine sulfate was used orally (½ grain [30 mg.] three times a day). Even when successful in aborting induced attacks, its effectiveness disappeared in from a half to one hour after a dose of 1 grain (60 mg.) of ephedrine. For ephedrine I therefore substituted the similar sympathomimetic drug benzedrine sulfate[4] on which I have previously reported in the treatment of sinus syncope.[5]

EFFECT OF BENZEDRINE SULFATE

Benzedrine sulfate in varying doses was given to 4 patients exhibiting the depressor response on stimulation of the carotid sinus (cases 1, 2, 3 and 4). At intervals after the administration attempts were made to induce syncope. The initial dose of benzedrine sulfate was 10 mg.; if this dose proved ineffective in preventing an induced attack the amount was increased 10 mg. at a time. From 20 to 30 mg. proved effective on many occasions and prevented the induction of syncope, but as much as 50 mg. in a single dose has at times been necessary.

The efficacy of benzedrine sulfate was demonstrable as early as twenty-five minutes after 10 mg. of the drug had been administered orally, but the hyperirritability of the sinus returned eighty minutes after the 10 mg. dose. Often, however, when 20 or 30 mg. was given, syncope could not be induced for as long as three and one-half to four hours. Thereafter the patients were given the effective amount of benzedrine sulfate at intervals slightly shorter than the period previously determined as necessary for the effect to wear off. Except for the instances to be noted, the depressor type of syncope could not be induced during the period extending from twenty-five minutes after the first adequate dose of benzedrine sulfate to three and one-half or four hours after the last dose. The average dose varied from 20 to 40 mg. three or four times daily.

In the first 3 cases (cases 1, 2 and 3) both spontaneous and induced seizures were absent during the period over which the effectiveness of benzedrine sulfate had been demonstrated. In case 4, although induced seizures were prevented by benzedrine, spontaneous seizures continued to occur occasionally. The patient in case 6 exemplifies the importance of meticulous study of patients with syncope due to a hyperirritable

4. The drug was furnished by the Smith, Kline and French Laboratories, of Philadelphia.

5. Robinson, L. J.: Benzedrine Sulfate in the Treatment of Syncope Due to a Hyperactive Carotid Sinus Reflex, New England J. Med. **217**:952-953 (Dec. 9) 1937.

carotid sinus reflex. Initially, pressure over either catotid sinus caused asystole, with apparently no change in the blood pressure prior to the complete disappearance of the pulse. However, after atropinization, which partially paralyzed the vagal effect, one readily discovered the masked hypotension as well as the bradycardia which preceded syncope. Therefore, had there not been a concomitant cerebral element, the patient would have fallen into the group amenable to sympathomimetic therapy.

In only 1 case was insomnia evident as the result of benzedrine therapy. In 1 case (case 1) a tolerance for benzedrine sulfate gradually became evident. At intervals of from seven to ten days it was necessary either to increase the dose or to omit the medication for several days.

A control series of patients with recurrent convulsions, none of whom possessed a hyperirritable carotid sinus, was also given benzedrine therapy. This group in no instance showed reduction in seizures.

CRITERIA FOR DIAGNOSIS OF THE CAROTID SINUS SYNDROME

Similarity of Induced and Spontaneous Seizures.—The fact that spontaneous and induced seizures are exactly alike is strongly in favor of the opinion that the carotid sinus syndrome is responsible for all seizures in a given case (cases 1, 2, 3 and 7).

Nature and Length of Auras.—Auras, such as vertigo, tinnitus, weakness, epigastric distress, hyperpnea, numbness or tingling of the extremities, anxiety, or any combination of these may herald either sinal or nonsinal syncope. When the aura precedes the syncope by hours or days the syncope is rarely of sinal origin. In sinal syncope the aura directly precedes the attack. It is to be remembered, however, that this short interval between premonition and seizure is also of common occurrence in nonsinal syncopal conditions, such as orthostatic hypotension, hyperinsulinism and "epileptic" seizures. When premonitory manifestations consist of hyperpnea, dysphagia or hoarseness, sinal syncope should be strongly borne in mind.

Position of Patient Prior to Syncope.—Sinal syncope nearly always occurs when the patient is vertical—usually when he is standing, occasionally when he is sitting—and only rarely while the patient is in the horizontal position. These observations and the fact that sinal syncope is abolished by the horizontal position illustrate the mechanism of cerebral anemia, whether due to vagal slowing, to hypotension or to unknown cerebral effects, on which the sinus syndrome in part hinges. Therefore, if orthostatic hypotension has been ruled out, seizures, which occur mostly while the patient is upright point strongly toward a sinus syndrome; conversely, seizures which occur mostly while the patient is horizontal point more strongly toward some other mechanism.

This is a relative rather than an absolute criterion in favor of the diagnosis of sinal syncope, as seizures due to other mechanisms may and do overtake persons in the vertical position as well as persons in the horizontal position. Furthermore, a patient with a hyperirritable carotid sinus, even while in the horizontal position, may exhibit convulsions and loss of consciousness on premeditated stimulation of the carotid sinus (as in cases 1 and 8) or on accidental stimulation of the sinus. In case 1 and 8, even when the patient was horizontal on a table, pressure over either carotid sinus produced typical sinal syncope on repeated occasions. In these 2 patients the degree of pressure, the length of time necessary to apply it and the intensity of the response were all exactly the same as when the patient was vertical.

Effective Stimuli.—Spontaneous sinal syncope may be brought on by patients through unintentional pressure on the hyperirritable carotid sinus, in the form of sudden movement of the head and neck, constricting neckwear or the swallowing of effervescent liquids. Roskam reported the case of a man with so sensitive a sinus that not only tight collars but even shaving over the region of the sinus precipitated convulsions.[1f] When such events are noted to precede seizures the sinus syndrome should be suspected. Their absence is of no aid, as spontaneous seizures due to a hyperirritable carotid sinus usually are not linked with any known specific stimulus.

In a patient with a hypersensitive carotid sinus reflex syncope can usually be induced by digital pressure over the hyperirritable carotid sinus. The suddenness and intensity with which pressure is made over the sinus are often decisive factors in the production of spontaneous as well as induced seizures. Gradual or light pressure frequently proves ineffective. Furthermore, if this mechanical stimulation is discontinued with the appearance of milder signs, such as early changes in color, pulse, blood pressure or localized clonus, complete syncope may not follow.

Even in patients known to possess the sinus syndrome. pressure over the sinus may at times be ineffective in demonstrating the phenomenon.

Duration of Syncope.—The duration of the unconscious state in a carotid sinus attack is generally short (from seconds to minutes), since the horizontal position into which the patient falls usually ends the syncope. Exceptions to this generalization occur, as in 2 reported cases [1e] in which attacks lasted as long as one hour, and in 1 of my own cases (case 8). In the latter, a state of repeated convulsions lasting two hours was initiated by pressure on the carotid sinus on one occasion.

Character of Attacks.—Syncope due to hypersensitivity of the carotid sinus is usually characterized by a sudden fall with (or, more rarely, without) convulsive movements. These movements are clonic and as a

rule generalized. However, with close observation I noted that induced convulsions began with clonus in the arm and leg contralateral to the sinus stimulated (cases 5 and 6), and even when paresthesia was manifest it was usually present in the contralateral arm (case 7). Limited contralateral clonus unaccompanied by further effects could be brought out clearly by releasing the pressure on the sinus as soon as arm clonus began. Several other cases (not included in this report) exhibited contralateral clonus without syncope. Urinary or fecal incontinence during a seizure may simulate "epileptic" convulsions, as Weiss and his colleagues,[1c] Smith and Moersch [1e] and I have observed.

Postsyncopal Features.—After sinal syncope the sensorium, as a rule, clears with remarkable rapidity. Moreover, postsyncopal confusion is apt to be absent, and even headache, vertigo and lassitude are rare. When sinal syncope is prolonged these features are, on the contrary, common. Thus, in case 8 isolated attacks, whether induced or spontaneous, and lasting only one minute, were followed by immediate recovery without after-effects. But when in the same case syncope was repeated at two minute intervals, coma and recurring convulsions ensued (often with incontinence), followed by postsyncopal fatigue, headache and drowsiness.

Frequency of Attacks.—Spontaneous sinal attacks may recur frequently (within hours or days) or relatively infrequently (months or years apart), so that this feature does not aid the diagnosis. As far as I could determine from my own cases, the successful induction of sinal syncope does not create a refractory state to repeated induction of syncope.

Effect of Phenobarbital.—The administration or withdrawal of ¾ to 1½ grains (40 to 90 mg.) of phenobarbital orally did not seem to alter the incidence of sinus seizures, either spontaneous or induced. Five grains (300 mg.) of soluble phenobarbital U. S. P. (sodium phenobarbital) was given intravenously in case 1 without lessening the ease of induction or the character of induced sinal syncope over a period of two and a half hours, despite marked somnolence. Weiss and Baker [1a] injected a sufficient amount of soluble phenobarbital intravenously to cause extreme somnolence without affecting the sensitivity of the carotid sinus reflex. Nevertheless, the 5 grain dose of soluble phenobarbital subcutaneously administered is credited by me with terminating status epilepticus induced initially by pressure on the carotid sinus (case 8).

In closing, the note of caution struck by Ask-Upmark [1g] may be sounded again. This is to the effect that indiscriminate extirpation of the carotid sinus, when performed without critical rationale for the purpose of abolishing epileptic seizures, is open to censure as well as to disappointment.

SUMMARY

Among 1,000 patients in the wards and in the outpatient department of a hospital for patients with epilepsy, the hyperirritable carotid sinus reflex was demonstrable in 9 patients, or 0.9 per cent of those tested.

Four patients presented a vagal and depressor response; 3 patients showed a vagal, depressor and cerebral response, and 2 patients showed a purely cerebral response.

A hyperirritable carotid sinus reflex seemed to be the sole mechanism underlying all seizures in 5 cases. Three patients exhibited a hypersensitive carotid sinus reflex and also were known to have an additional convulsive mechanism. The ninth patient with a hyperirritable carotid sinus reflex probably had an additional convulsive mechanism.

The ages of the 1,000 patients tested ranged between 4 and 82 years. The ages of the patients with the sinus syndrome ranged between 14 and 71 years. All but 1 were males.

Benzedrine sulfate prevented syncope when the hyperirritable carotid sinus reflex exhibited a vagal and depressor response.

PROGRESSIVE CONFUSIONAL SYNDROME ACCOMPANYING INJURIES OF THE CERVICAL PORTION OF THE SPINAL CORD

TRACY J. PUTNAM, M.D.
BOSTON

After fracture of the cervical portion of the spine with injury to the cord, mental symptoms are sometimes observed. They are often ascribed to cerebral injury, alcoholism or the effects of medication, and it is usually difficult to be certain that they are not due to one or another of these factors. Occasionally, however, cases occur in which the mental symptoms develop late or persist under circumstances which make it appear that the cervical injury is in itself responsible for the symptoms.

An example is the following case, reported by permission of Dr. W. J. Mixter.

CASE 1.—*Clinical History.*—F. M., a chauffeur aged 29, previously healthy, apparently fell from a balcony about 30 feet (9 meters) high, while drunk, some time during the night of Sept. 3, 1933. He was found on the ground at 9:30 the following morning, conscious but paralyzed from the neck down, and without memory of what had happened. He was brought to the Massachusetts General Hospital the next day, where it was found that there was tenderness over the fourth to the seventh cervical spine. He could move his arms feebly, his legs not at all. The deep reflexes in the arms were hyperactive and the knee jerks sluggish. There was a normal plantar response on both sides. There was anesthesia from the shoulders down, except for some sensation over the penis and scrotum. Lumbar puncture showed a dynamic block and bloody fluid. The temperature was 102 F., the pulse rate 85, the respiratory rate 18 and the blood pressure 180 systolic and 90 diastolic.

Of particular interest was the mental state. The patient was cooperative, alert and anxious, but was unable to remember the accident or the events leading up to it and could not even give a reliable past history. He did not know where he was or why he had been brought there and had difficulty in recognizing persons who should have been familiar to him. There was no odor of alcohol on his breath, no contusion of the scalp and no deformity or roentgenographic evidence of fracture of the skull.

There was almost complete paralysis of the intercostal muscles, but diaphragmatic respiration was regular and apparently ample. There were a few rales at the base of each lung. The color of the mucous membranes showed no more than a hint of cyanosis.

From the Neurological Unit of the Boston City Hospital and the Department of Neurology, Harvary University Medical School.

Read by title at the Sixty-Fourth Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 2-4, 1938.

At the time when the patient was seen, the danger and futility of laminectomy during the acute stage of fracture of the cervical portion of the spine were not appreciated. The spinal block was taken as an indication for operation, which was carried out with local anesthesia late on the afternoon of September 5. A contused, edematous cord, without a gross hematoma, was exposed. During closure of the wound respiration ceased.

Autopsy.—The lesion was limited to the last three cervical segments. No gross lesion of the brain was observed.

In this case there was no history of chronic alcoholism or other deteriorating disease, and the progression of mental symptoms and their character were not suggestive of a primary injury to the brain. It is possible, therefore, that the confusion and delirium were in some way the result of the cervical injury. A survey of the records of other cases of fracture of the cervical portion of the spine leaves one usually in doubt as to the part played by complicating factors, but in the following cases of operative and pathologic injury cerebral trauma at least could be excluded.

CASE 2.—*Clinical History.*—P. D., a carpenter aged 65, was first admitted to the neurosurgical service of the Boston City Hospital on Jan. 13, 1930, with the complaint of severe pain in the left hand and foot of two years' duration. There was a history of an injury to the head some time before, but there had been no sequelae until the presenting symptoms developed. Examination revealed nothing remarkable except a mild parkinsonian posture and facies, tremor of the left hand and slight left hemiparesis. No cause for the pain was found, but the patient was evidently in constant misery and could not sleep even with large doses of sedatives. A diagnosis of central (thalamic?) pain was made, and the patient was informed that there was no prospect of relief. He begged to have something done, however, no matter how small the chance of success. A nerve block of the hand and, later, cortical exploration were carried out, without change in the patient's symptoms. As spinal anesthesia gave him relief, it was proposed to perform cervical chordotomy. This was carried out on Feb. 6, 1931. The right spinothalamic tract was severed at about the third cervical segment, and the left, at the fourth cervical segment. The operation was performed without difficulty, but there was considerable loss of blood, as the patient had some hypertension. He seemed in a satisfactory condition at the end of the operation, and transfusion was not deemed necessary.

On the following day his general condition appeared satisfactory and the pain was relieved, but he was restless. Movements of the right side of the chest appeared slightly embarrassed, but there was no sign of pulmonary involvement. The restlessness became delirium, at first mild but later difficult to control. Sedatives seemed to make it worse. Respiration became irregular; the patient became disoriented and apparently hallucinated. Terminal pulmonary rales appeared, and he died eleven days after the operation. The temperature remained normal.

Autopsy.—There was slight atrophy of the basal nuclei. The operative wound and cord were in satisfactory condition. There was no consolidation of the lungs.

CASE 3.—*Clinical History.*—A. P., a woman aged 62, referred by Dr. Stanley Cobb, was first seen in January 1933. She had contracted herpes zoster of the left axilla six years previously and had been tormented by severe neuralgia since—

so severe that she took up to 0.15 Gm. of morphine tartrate daily for relief. A course of roentgen treatments and a subarachnoid injection of alcohol gave no relief. After long delay and much consideration, chordotomy and section of the nerve roots were decided on. This was carried out on May 25, 1933, at the Phillips House, Massachusetts General Hospital. The spinothalamic tract was severed at the third cervical segment on the right, and the posterior roots of the fourth, fifth and sixth cervical nerves were sectioned on the left. The operation was long, but the patient appeared in good condition at the close, except for slight depression of thoracic respiration.

On the following day and subsequently she complained of neuralgia, although the scar, which had been extremely tender, was no longer so. On account of a rectal fissure, she demanded morphine as before for relief from the neuralgia. An attempt was made to replace morphine with phenobarbital, without success. She became extremely constipated but would not permit administration of enemas. As the days passed it became evident that she was becoming more disoriented. She asked why she had been taken to Japan and failed to recognize her attendants. She also wished to know when the operation would be performed.

Although the temperature, pulse and respiration remained normal and the wound was in satisfactory condition, it became evident after three weeks that some drastic step must be taken to abolish the morphine habit, dilate the anal sphincter and evacuate the rectum. With the advice and help of a medical consultant, she was given 0.3 Gm. of sodium amytal intravenously. This induced light sleep, and it was possible to omit the morphine and to evacuate a large quantity of impacted feces.

About twelve hours after administration of the hypnotic, the respiratory rate began to rise, finally reaching 40 a minute. On the following day the temperature and pulse rate also rose, and without recovering consciousness she died.

Autopsy.—The wound and cord were in good condition; there was no gross lesion of the brain and only mild atelectasis of the lungs.

CASE 4.—*Clinical History.*—M. G., aged 56, was referred by Dr. Colket Caner and Dr. Roger Lee on account of bilateral athetosis and torticollis. The patient was in good health until the age of about 20, when he began to have difficulty in walking. The disease progressed steadily; the arms became involved, and he was entirely disabled before he was 30. When first seen in October 1934 he could walk only with the greatest difficulty and could not sit or lie still. He could not feed or dress himself without assistance. He was so miserable that he often threatened to commit suicide. His mentality was intact, and he was thoroughly well informed and cooperative. The possibilities and dangers of chordotomy of the extrapyramidal tracts for relief from the athetosis [1] were explained to him; after long consideration, he decided to have the operation performed.

The operation was carried out on Dec. 11, 1935, at the Phillips House. The left anterior column was sectioned at the third, and the right at the fourth, cervical segment. The first two anterior roots on each side were cut. Both spinal accessory nerves were cut through separate incisions in the neck.

---

1. Putnam, T. J.: Results of the Treatment of Athetosis by Section of the Extrapyramidal Tracts in the Spinal Cord, Arch. Neurol. & Psychiat. **39**:258 (Feb.) 1938.

The patient made an excellent recovery and sat quietly in bed for the first time in many years. Movements of the chest were slight, but respirations were of normal rate and appeared ample. The color was good, but perhaps a trifle purplish.

Two days after operation he began to be a little restless and was occasionally disoriented for place. Usually extremely cooperative, he began to be difficult to care for. Small doses of phenobarbital and of morphine appeared to make matters worse. Still, no particular concern was felt until a week after operation, when it was time to remove the sutures. This simple procedure appeared to cause undue resentment and fatigue. The following day his color was distinctly worse, and the respiratory rate began to rise. He was placed in an oxygen tent, without relief. The pulse increased in rate, became extremely weak and finally failed.

Autopsy.—The site of the wound was in good condition. There was some atelectasis, but no evidence of infection of the lungs. Aside from inconspicuous cellular losses in the basal ganglia, no evidence of disease was observed in the brain.

In the following 3 cases, studies on the gases of the blood were secured.

CASE 5.—*Clinical History.*—T. D., aged 55, was admitted to the neurologic service of the Boston City Hospital on Sept. 3, 1936, with a complaint of pain in the back, of two months' duration, and weakness of the extremities. The reflexes were absent. There was a band of hypesthesia from the seventh to the tenth dorsal segment. Spinal puncture showed complete block and a yellow fluid. There developed embarrassment of thoracic respiration, and the patient became drowsy, slow, incoherent and disoriented. Study of the arterial blood at this time showed that the oxygen content was 12.8 volumes per cent, the oxygen capacity, 15.75 volumes per cent, the oxygen saturation 80.9 per cent and the carbon dioxide content 42.84 volumes per cent. The hemoglobin was 77 per cent and the red cell count, 3,890,000.

The patient improved slightly when placed in a respirator, but there developed signs of pulmonary consolidation; he became comatose and died on September 19.

Autopsy.—There was a reticulum cell sarcoma of the upper thoracic portion of the cord. Sections from the brain revealed no abnormalities.

CASE 6.—*Clinical History.*—T. G., aged 65, who was known to have been an alcohol addict at one time, was transferred to the neurologic service of the Boston City Hospital on July 17, 1936, with the history that three days previously he had felt a "shock" in the right arm and that shortly thereafter paraplegia developed. On admission to another service of the hospital within a few hours after the onset of paralysis, he was reported to be rational. On the following day he became combative, disoriented for time, place and person, profane and apparently hallucinated. He lay with the arms flexed. There was complete paraplegia, with retention and sensory loss up to the level of the fourth cervical segment. There was no thoracic respiration, but movements of the diaphragm were vigorous. The color and pulse appeared satisfactory. Lumbar puncture showed a yellow fluid, containing 25 lymphocytes, with evidence of spinal block. The hemoglobin was 65 per cent, and the red cell count, 3,200,000. The patient was placed in a Drinker respirator, but this produced only slight improvement in the general condition.

Studies of the gases of the blood were made on July 17. Values for arterial blood were: oxygen content, 13.92 volumes per cent; oxygen capacity, 16.67 volumes per cent; oxygen saturation, 83.9 per cent, and carbon dioxide content, 46.97 volumes per cent. Values for venous blood were: oxygen content, 7.83 volumes per cent; oxygen capacity, 16.67 volumes per cent; oxygen saturation, 46.9 per cent, and carbon dioxide content, 50.15 volumes per cent. On the following day, while the patient was still in the respirator, the arterial blood showed: oxygen content, 14.03 volumes per cent; oxygen capacity, 15.92 volumes per cent; oxygen saturation, 88.1 per cent, and carbon dioxide content, 42.99 volumes per cent. The patient was then taken out of the respirator temporarily. Eight minutes later, a sample of arterial blood showed: oxygen content, 13.84 volumes per cent; oxygen capacity, 15.92 volumes per cent; oxygen saturation, 86.9 per cent, and carbon dioxide content, 43.15 volumes per cent.

The patient died on July 18, without much change in the pulse or respiratory rate.

Autopsy.—There was hematomyelia of the cervical portion of the cord, apparently of spontaneous origin. There was no gross lesion in the brain. The lungs showed no evidence of pneumonia.

CASE 7.—*Clinical History.*—K. B., a man aged 55, was admitted to the neurologic service of the Boston City Hospital on July 26, 1937, with a history of sudden onset of generalized weakness five days before, which gradually became definite paraplegia, with retention of urine and a sensory level at about the fifth cervical segment. There was some limitation of movement of the chest, but respirations appeared adequate. Roentgenograms showed what might be interpreted as an old fracture of the lower cervical vertebrae, and spinal puncture revealed a partial block but normal fluid.

Of particular interest was the mental condition. The patient appeared somewhat anxious, had difficulty in recalling recent and distant events and gave a confused and contradictory history. He was partially disoriented for time and place and somewhat restless and gave evidence of having mild delusions. There was some arteriosclerosis, but no obvious cause for confusion. The mucous membranes at this time were deep red, with only a hint of cyanosis. The hemoglobin was 77 per cent; the red cells numbered 4,100,000, and the white cells, 8,500.

Arterial blood was drawn from the brachial artery on July 28. Examination showed (average of two determinations): oxygen content, 17.6 volumes per cent; oxygen capacity, 19.1 volumes per cent; oxygen saturation, 91.1 per cent, and carbon dioxide content, 45.3 volumes per cent.

Traction was applied to the neck. The general condition and respiration immediately improved, and the mental confusion disappeared. The paraplegia also improved up to a certain point, but then remained fixed. The spinal block gradually became more marked. The patient refused operation for several months, but an exploration was performed on November 23. An extradural tuberculoma was disclosed and partially removed. The patient died of tuberculous meningitis on November 30.

COMMENT

A group of 7 cases is reported in which symptoms of confusion, disorientation, delirium and mild hallucinations developed several hours or days after injury to the cervical region of the spinal cord. All but 1 of the patients was over 50 years of age; 2 (cases 1 and 7) were distinctly arteriosclerotic; 1 (case 2) was a morphine addict, and 1

(case 6) had suffered from alcoholism. In all, the mental symptoms developed acutely only after injury to the spinal cord. The psychiatric symptoms were so uniform that they may well be grouped together under a term such as "the progressive confusional syndrome." The question naturally arises: What mechanisms may account for the symptoms?

No definite answer can be given to this question at present. There is evidence, however, which suggests that the symptoms are due to a deficient supply of oxygen to the brain. First, they resemble closely the effects of anoxia of various types. A clear example is mountain sickness. Peters and Van Slyke [2] summarized the effect of decreasing oxygen pressure in the inspired air on a normal resting subject as follows: With from 16 to 12 per cent of an atmosphere: "Accelerated pulse and respiration. More than usual effort required for concentration. . . ." With from 14 to 9 per cent: "Judgment faulty. Emotions such as hilarity and pugnacity, easily roused and unstable. . . . Muscular effort causes quick fatigue, and may injure heart. Fainting may occur. . . . Typical of alcoholic intoxication." With from 10 to 6 per cent: "Subject becomes unconscious. If in fit physical condition, coma is cerebral with 'rigid, glassy-eyed' unconsciousness. . . . If less fit, cardiac syncope occurs before cerebral. Dazed mental state prevents realization of danger as coma comes on."

The type of death from cardiac failure resembles that described in conditions of asphyxia. A similar phenomenon was observed by Alexander and MacDonald [3] in experimental electric shock. In many animals (cats) both respiration and cardiac output were reduced, and the heart stopped before the respiration. If artificial respiration was given, however, cardiac failure was prevented. Cardiac failure occurred in acute experiments carried out by Sands and DeGraff [4] on pigs breathing mixtures of nitrogen and oxygen at a level of about 9 per cent. In febrile animals failure occurred at a still higher level.

In 2 of the cases reported (cases 5 and 6) the oxygen level of arterial blood approached that (13.19 volumes per cent) at which Lennox, Gibbs and Gibbs [5] observed acute unconsciousness in 1 of their otherwise normal subjects breathing a mixture of nitrogen, and was presumably below that at which Barcroft experienced mental symptoms after a pro-

2. Peters, J., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1935, vol. 2, p. 588.

3. Alexander, L., and MacDonald, M.: Personal communication to the author concerning work in progress.

4. Sands, J., and DeGraff, A. C.: The Effect of Progressive Anoxemia on the Heart and Circulation, Am. J. Physiol. **74**:416, 1925.

5. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Relationship of Unconsciousness to Cerebral Blood Flow and to Anoxemia, Arch. Neurol. & Psychiat. **34**:1001 (Nov.) 1935.

longed stay in a low pressure chamber.[6] Goralewski [7] reported on an experiment with over 100 subjects, 22.2 per cent of whom experienced mild mental symptoms in an atmosphere containing from 18 to 22 per cent of oxygen. The symptoms increased with prolonged exposure. In all these observations it is obvious that the effect of mild deprivation of oxygen may be slowly cumulative. An excellent review of the subject is given by MacFarland.[8]

In cases of chronic anemia lower oxygen tensions are encountered, but are apparently compensated for in part by increased respiration and accelerated circulation. Compensatory physiologic changes also occur in subjects living at high altitudes, but if they are inadequate, chronic mountain sickness with mental symptoms may occur.[9]

Deficient saturation of the blood due to low oxygen pressure, pulmonary disease or inadequate respiration (anoxic anoxia) is, however, not the only possible type of anoxia. A second type is anemic anoxia,[2] due to deficient oxygen capacity of the blood. The similarity of the symptoms described to those of acute hemorrhage needs no comment. In all the cases in which the symptoms developed after operation, in cases 5 and 6 and in many instances of traumatic fracture of the spine, hemorrhage or anemia probably contributed to the symptoms. Surgical shock alone, however, rarely gives rise to such slowly progressive mental symptoms as these.

A third type of anoxia is the stagnant variety, due to cardiac weakness, low blood pressure or peripheral obstruction (for example, from arteriosclerosis). The symptoms observed in the group of cases reported are suggestive of some resulting from cardiac decompensation.[10] It is likely that limitation of motion of the chest embarrasses venous return and conceivable that interruption of nerve pathways to or from the heart may hinder adaptation. Vascular dilatation often occurs below an injury to the cord.

Finally, tissue anoxia may result from certain drugs and poisons, such as opiates, alcohol, anesthetics and hypnotics.[11] The drug addiction in case 3 and the alcoholism in case 6 were perhaps partly responsible for the development of symptoms. Restlessness is sometimes paradoxi-

---

6. Barcroft, J.: Lessons from High Altitudes, in The Respiratory Function of the Blood, Cambridge, England, Cambridge University Press, 1925, pt. 1.

7. Goralewski, G.: Anoxämie und Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **158**:83, 1937.

8. MacFarland, R. A.: The Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behavior, Arch. Psychol., 1932, no. 145.

9. Monge, C.: High Altitude Disease, Arch. Int. Med. **59**:32 (Jan.) 1937.

10. Riesman, D.: Acute Psychosis Arising During the Course of Heart Disease, Am. J. M. Sc. **161**:157, 1921.

11. Jowett, M., and Quastel, J. H.: The Effect of Narcotics on Tissue Oxidations, Biochem. J. **31**:565, 1937.

cally increased by sedatives; this was particularly noticeable in cases 2, 3 and 4. The high death rate from laminectomies for fracture of the cervical region of the spine may be due in part to the effect of the anesthetic.

Unquestionably, several types of anoxia may coexist and exert a cumulative effect. Such an explanation, if any, must be invoked to account for the symptoms in case 7, in which the arterial level of oxygen and the red cell count were only slightly low, but in which there were evidences of circulatory embarrassment which could not be compensated for by increased ventilation. Certainly, the improvement with more adequate respiration was striking.

The possible effect of long-continued elevation of the level of carbon dioxide in the arterial blood, as a result of atelectasis, also deserves consideration.

An alternative explanation may be that the wound in the cord produces ascending edema, which finally affects some of the "vital centers" of the brain stem. No anatomic evidence, however, of such a change was seen in the cases at autopsy, nor was edema observed by Alexander [12] in the spinal cords of a series of patients dying after an interval from fracture of the cervical portion of the spine. Moreover, a suggestively similar syndrome has been seen in at least one case of polyneuritis involving the intercostal muscles, and the mental symptoms were partially relieved by artificial respiration in the Drinker apparatus.

Obviously, still other explanations are conceivable, and the subject is open for speculation until further facts are available.

Certain preliminary conclusions in regard to the treatment of injuries of the cervical portion of the cord appear justified. First, the possibility of development of such a syndrome, with the risk it appears to imply, should be weighed before cervical chordotomy is decided on. The actual danger involved is illustrated by a group of 25 patients on whom cervical chordotomies were performed for athetosis (thirty operations in all, since some were done in two stages), with 3 deaths. The deaths all occurred after bilateral operations, which were performed in 12 instances.[1] No deaths have occurred, however, since a special watch has been kept for the milder signs of respiratory embarrassment.

Second, if respiratory or circulatory failure of any type plays a part in the production of the syndrome, any operation on patients known to have a cervical injury and showing a confusional syndrome or severe limitation of respiratory movements should be avoided unless absolute indication for it exists. In cases of fracture of the cervical portion of the spine, for example, it is my experience that operation during the acute stage almost always accelerates death and has never been of

12. Alexander, L.: Personal communication to the author.

definite benefit. If an operation of some type is unavoidable, the use of artificial respiration by means of intratracheal tube should be considered.

Third, if the confusional syndrome develops it should be taken as an ominous sign, and steps should be taken to improve respiration. The use of an oxygen tent may be tried, but it is usually not as satisfactory as a Drinker respirator. The use of a respirator is sometimes attended by difficulties, as the patient may refuse to accept its rhythm. Even milder grades of anemia should be combated by transfusion. While these measures have not been extensively used in the treatment of the confusional syndrome, they have proved useful for relief from other symptoms of respiratory embarrassment in cases of injury to the cervical portion of the cord.

SUMMARY AND CONCLUSIONS

1. After fracture of the cervical portion of the spine with injury to the cord, mental symptoms sometimes appear, as in a case cited. Such symptoms are often attributed to a cerebral injury, delirium tremens or other cause.

2. A series of 6 cases is reported in which a fairly consistent psychiatric syndrome, consisting of forgetfulness, disorientation, hallucinations, delirium and often death from cardiac failure, has supervened in cases of injury to the spinal cord without cerebral trauma.

3. It is suggested that the symptoms may be due to a mixed type of anoxia, in which embarrassment of respiration, moderate in itself, may limit compensation for anemia, low blood pressure or cerebral vascular disease.

4. The term "progressive confusional syndrome" is suggested for the condition.

THERAPEUTIC USE OF CURARE AND ERYTHROIDINE HYDROCHLORIDE FOR SPASTIC AND DYSTONIC STATES

MICHAEL S. BURMAN, M.D.

NEW YORK

The specific effect of curare was demonstrated by Bernard [1] in 1857. It is agreed that the peripheral paralysis caused by curare is due to block of nervous impulses at the myoneural junction. The demonstration of this specific effect led to the use of curare from 1857 to 1867 in the treatment of convulsive conditions, such as epilepsy, rabies, tetanus, chorea, strychnine poisoning and various tics.[2] Curare was quickly discredited because of ignorance of action of the drug, timidity in its use, improper dosage and spacing of doses (since the effect of the drug is transient) and the fact that unassayed curare or curare of poor quality was used.

The aforementioned conditions do not constitute the field of indication for curare. The medicament has a specific place in drug therapy, in which its specific action is utilized. This is the reduction of spasm and plastic muscular rigidity in patients with spastic paralysis and allied conditions.

The most recent investigation of the action of curare on paralytic rigidity in man is that of West (1931-1935). He treated 30 patients with thirty year old curare.[3] The drug was dissolved in water and put up in ampules. The dose ranged from 2 to 20 mg. Certain untoward symptoms, which can be attributed in part to the presence of curine, were noted. The curine in curare does not have the effect of curare but acts on the circulation. From ten to thirty minutes after injection, headache and slight giddiness occurred, which were worse on standing. These symptoms were coincidental with a drop in systolic blood pressure of 20 mm. of mercury and a fall in pulse rate to 60 or lower, in patients

From the Hospital for Joint Diseases, the Service of Dr. Leo Mayer.

Read at the meeting of the Boston Society of Psychiatry and Neurology, Oct. 20, 1938.

1. Bernard, C.: Note sur la curarine et ses effets physiologiques, Bull. gén. de thérap. **69**:23, 1865.

2. Jousset: Du curare au point de vue thérapeutique, Bull. gén. de thérap. **69**:294 and 396, 1865.

3. West, R.: (*a*) Pharmacology and Therapeutics of Curare and Its Constituents, Proc. Roy. Soc. Med. **28**:565, 1935; (*b*) Pharmacological Study of Derivatives of Two Specimens of Tubo-Curare, and Examination of Four Members of Genus Strychnos and One Rubiaceous Plant Associated with Curares of British Guiana, Arch. internat. de pharmacodyn. et de thérap. **56**:81, 1937.

with a normal pulse rate of 80. Nonpersistent lateral nystagmus was present in some patients, with associated giddiness. When the giddiness was marked the patient was confused and ataxia was present. From 5 to 10 minims (0.3 to 0.6 cc) of epinephrine successfully counteracted all this.

The muscle-relaxing effect of curare was also demonstrated by West. No effect of the drug was noted in cases of epilepsy or in 2 cases of arterial hypertension with arteriosclerosis. A favorable result was obtained in a case of causalgia of the upper extremity. West noted that curare reduces the rigidity of parkinsonism. He has used it also for paraplegia in flexion due to syphilitic myelitis, for vascular hemiplegia (2 cases), for multiple sclerosis with spastic paraplegia, for spasm of the orbicularis muscle of the eye and for other conditions. A girl aged 13 with spastic hemiplegia present since birth showed favorable results after curare therapy. Symptoms were not obtained till a dose of 12 mg. had been reached. The child had spontaneous athetoid movements at times, and the arm would assume unusual postures. After administration of 12 mg. of curare the arm was flaccid at the side. Passive flexion presented no resistance, and extension occurred to an extent not previously achieved.

Curare has been tried for various spastic conditions, such as pyramidal contracture, parkinsonism, spasmodic paraplegias of various origins, myoclonia, multiple sclerosis with spastic paraplegia, spasm of the orbicularis muscle of the eye and other conditions.[4] Tsocanakis,[4a] a pupil of Pierre Marie, used the bromhydrate of cicutine (conium or hemlock) also. West abandoned the use of a synthetic quaternary ammonium base, octyl trimethyl iodide, since it achieved no therapeutic result and produced vomiting in man. Such ammonium bases have a curare-like action. There are many other drugs with curare-like action, for example, methyl strychnine and amyl quinine, which have not been used therapeutically in man.[3b]

Curarine, an alkaloidal derivative of curare, has an action like that of curare. West pointed out that its margin of safety is small and that it relaxes muscle only in the sense that it paralyzes it.

This article outlines my clinical experience with curare in 19 cases of spastic paralysis. It is empiric in the sense that it has dealt more with clinical observation than with precise methods of laboratory study, such as action currents and measurements of tonus. I have been interested in the gross effects of curare, which the patient himself is equally

4. (*a*) Tsocanakis, G. D.: De l'action thérapeutique du bromhydrate de cicutine et du curare dans les états spasmodiques, Thesis, Paris, no. 211, Paris, Amédé LeGrand, 1923. (*b*) Kairiukschtis, V., and Kutorga, V.: Versuche die Muskelrigidität beim Parkinsonismus durch Injektion von Kurare zu beseitigen, München. med. Wchnschr. **74**:537, 1927.

able to note. The point of view of this study is orthopedic, which means that the investigation has been reconstructive rather than neurologic. Most of the patients were examined and the diagnoses confirmed by a neurologist. The deficiency of the study from the neurologic point of view may be the absence of a precise interpretation of the neurologic status after the administration of curare. This work should be done by a competent neurologist.

Curare in proper doses acts first on the hyperinnervated muscles. This has been demonstrated experimentally by Frederic Bremer,[5] who proved that the drug exhibits an elective action in the reduction of the rigidity of local tetanus and of decerebrate rigidity. The normal muscular tone of an intact animal is not so electively sensitive to curare. Bremer noted an antagonism between curare and epinephrine. The motor innervation of tonus and reflex rigidities is especially made up of impulses of high frequency but of subnormal amplitude, and these are more easily blocked than impulses of smaller frequency at the curarized myoneural junctions. The pathway of tonic and phasic impulses is necessarily the same, but even at an initial stage of curarization motor impulses of tonic innervation can be stopped when impulses of smaller frequency and of greater amplitude still pass the myoneural junction to stimulate muscle fiber. Bremer's work has been confirmed by de Almeida and Moussatché.[6]

The action is peripheral at the myoneural junction on impulses which pass through the common pathway of the motor nerve. No deafferentation takes place as a result of curare therapy. Matthews found no modification in the ascending discharge from the muscle spindle resulting from curarization in any dose inadequate to cause paralysis. Study of the action current of spastic muscles indicates that a hyperinnervated muscle shows great frequency of impulses of varying, but usually high, amplitude (Steindler and Lindemann[7]). The experimental convictions of Bremer are supported by clinical evidence.

MATERIAL

The curare which I used was supplied by the Merck Institute of Therapeutic Research. (Despite world-wide search, only a limited quantity of curare has ever been available at one time, and in the last year there has been none.) Repeated toxicity test with this curare, carried out by the Merck Institute, indicated

5. Bremer, F.: The Tonus and Contracture of Skeletal Muscles, Arch. Surg. **18**:1463 (April) 1929.

6. de Almeida, O., and Moussatché, H.: Action du curare sur les contractures, Compt. rend. Soc. de biol. **117**:499, 1934.

7. Steindler, A., and Lindemann, E.: Alterations of the Action Current of Skeletal Muscles Following Sympathetic Ramisection, J. Bone & Joint Surg. **11**: 1, 1929.

that the lethal dose for white mice is 4.4 mg. per kilogram of body weight. This dose has repeatedly killed 50 per cent of the animals tested. The curare was prepared in rubber-stopped ampules. Each ampule contained 50 mg. of curare dissolved in 10 cc. of sterile water. This made a slightly cloudy, light brown solution, in which there was sometimes a small amount of sediment. To put it more simply, each cubic centimeter of solution contained 5 mg. of curare. The solution was sterilized fractionally, filtered through a Berkefeld filter and placed in sterile ampules. After filling, a few ampules were tested and found to be sterile. The ampules contained no preservatives, such as phenol or cresol. These ampules have preserved the sterility of the curare contained in them, except in a few instances in which the substance became contaminated with molds or bacteria. The solution cannot be considered, therefore, as self sterilizing. The drug is best kept at room temperature in some darkened spot.

This curare has been well and uniformly standardized. Such standardization can be accomplished only by biologic assay, as with digitalis and ergot, since curare is not a simple drug but a variable compound.

DOSAGE

Curare is administered either intramuscularly or intravenously. The dose [8] varies from patient to patient, depending on the two factors of weight and extent of spasm and muscular rigidity. The larger doses, therefore, have been given to dystonic persons. The average dystonic patient requires about 25 mg. intravenously. When I have exceeded this dose I have always proceeded cautiously, raising the amount 1, 2 or even 5 mg. at a time by estimating the reaction to the drug. Adult spastic or dystonic patients take larger quantities of the drug by reason of greater weight and (sometimes) greater spasm. The intramuscular route is preferred. When the amount of fluid to be injected exceeds 8 cc. it is best to administer it intravenously. I have usually given smaller amounts into the buttocks. Local reaction has not been noted.

A hemiplegic patient weighing less than 120 pounds (54.4 Kg.) may require a dose between 10 and 40 mg. intramuscularly. The amount of the drug to be injected intravenously is about half that required for intramuscular injection.

The dose is calculated individually for each patient. One begins with a small and relatively ineffective dose and increases this to the stabilizing dose. This is the maximum amount of the drug to be administered at a single injection and it should not be exceeded. No exact dose can be prescribed, but a little experience will help in estimating the range for each patient.

Increasing the dose gives increasing effect, but clinically this is of use only up to the point at which the symptoms referable to the cranial nerves become too unpleasant. This curare is so finely assayed that it is quantitatively exact to the milligram.

---

8. It must be understood that the doses mentioned are for the spastic and not for the normal person. It is likely that such doses would be toxic to a normal person.

The excretion of curare is rapid, taking place within about two hours. The dose, therefore, must be repeated. Correspondingly, if too large a dose should be administered the period of recovery from this, too, would be short.

EFFECTS

The duration of therapeutic effect is from one to two days as a rule, so that an injection should be given at least three times weekly. The first effect appears in from twenty to thirty minutes after the intramuscular injection. The effect is immediate on intravenous injection, beginning even before all of the solution has been injected; hence the necessity of gradual injection. Curare "hits" as if by a direct blow on intravenous injection, and this is directly proportionate to the amount given. Relaxation is at a peak immediately but drops rather quickly, so that the effects of the drug may no longer be manifest after four hours. After intramuscular injection it falls more slowly from a more sustained plateau.

In spite of this I have been repeatedly struck with the prolonged action of curare. It seems to exert its action even after twelve days or longer. This is not in accord with its rapid excretion but is true clinically. If the drug is taken at regular intervals an overlap effect is present, so that there is never a return to the original level of spasticity. The prolonged effect can be explained only on the basis of a more or less permanent change at the myoneural junction, induced by curare.[9]

Repeated administration of curare is not harmful, nor do increasing doses become necessary for a constant effect. Steiner noted the opposite in rabbits and dogs. He believed that these animals became tolerant to curare, needing larger doses on repetition for effect.

"Central" symptoms, or symptoms referable to the cranial nerves, are not unusual after doses of more than 20 or 30 mg. given intramuscularly; they are invariably manifest when an effective intravenous dose is given. With smaller doses such symptoms are not constant. It may be that symptoms are produced by 20 mg. of curare in one patient and not in another of approximately the same status; even in the same patient, repetition of a similar dose may not cause the repeated appearance of symptoms. Such symptoms, in general, are quantitatively proportionate to the dose used when the limit of inconstant effect is passed. An experienced observer should be able to guess approximately the dose given.

---

9. Dr. Paul Hoefer and Dr. Tracy J. Putnam noted changes in the electromyogram which persisted even up to twenty-four hours after injection of curare.

The patient becomes dizzy. His eyes feel "fluttery." It is difficult for him to open his eyes because of heaviness of the lids. As the dose is increased the symptoms increase. He keeps the lids tightly closed and finds it increasingly difficult to open them. Diplopia is not uncommon. Dizziness may become so marked that the patient may not be able to walk with certainty. He feels befuddled and as if he were drunk. With large intravenous doses (above 30 mg.) certain alarming symptoms occasionally appear. Just after the injection, or even during it, the face assumes an expression of stupefaction, the mouth is held partly open, and saliva may drool from the mouth. The color of the face is ashen gray. The eyes are held half closed, and their expression is fixed. The head hangs heavy and limp and may fall to one side as if the muscles of the neck found the burden of the head too great. The throat feels constricted. The patient walks as if drunken and cannot take more than a few steps unsupported. He is extremely dizzy and "sees double." Breathing is not disturbed. His limbs feel weak. He lies in bed, looking upward with blank eyes. I have noted these alarming symptoms in 2 instances, on the intravenous administration of 32 and 35 mg., respectively, of curare. Such manifestations are alarming but fortunately pass away very rapidly, so that the patient's safety is assured in a few minutes. He is well again after fifteen minutes. However, I have given from 50 to 60 mg. of curare intravenously to an adult and have observed only the usual mild to moderate heaviness of the eyes, some dizziness and slight facial masking.

These alarming symptoms, it must be stressed, fall outside the field of therapeutic administration of curare. Even in the dystonic patient they need not occur if care is taken in calculating the dose, nor should enough curare ordinarily be administered to produce them. The usual slight symptoms are well tolerated by the patient, who may even welcome them as an index of the activity of the drug.

The pupils are not ordinarily affected but may be moderately or widely dilated with larger doses. Nystagmus is seldom present. The pulse and blood pressure are unaltered, indicating that the curare used is free of curine. Glycosuria attributable to curare was not present after an intramuscular dose of 40 mg.

The "central" effects do not last more than thirty minutes, as a rule. The patient may be kept in bed until the symptoms subside. I have used epinephrine on several occasions to combat such symptoms on the basis of the experimental evidence presented by Bremer of an antagonism between curare and epinephrine and the clinical experience of West. I have given 0.5 cc. of a 1 : 1,000 solution subcutaneously, as a rule, with but slight effect. In 1 case an increase of spasticity with generalized muscle tremor developed after administration of 7 minims (0.43 cc.) of epinephrine. The Babinski sign (not previously noted)

appeared, together with sustained ankle clonus. The epinephrine had no effect on the symptoms referable to the cranial nerves.

In a few cases, at the suggestion of Dr. Charles Sutro, I used prostigmine in ordinary therapeutic doses to antagonize the curare administered. Prostigmine is a synthetic homologue of physostigmine. Its antagonism to curare has been demonstrated experimentally by Rosenblueth, Lindsley and Morison [10] and by Briscoe.[11] With the limited doses given, prostigmine had no antagonistic effect on curare.

EFFECT OF CURARE ON MUSCLE

It is not possible within the therapeutic range of administration of curare to render a limb completely flaccid. This can be done only with toxic doses. However, there does occur an elective release of plastic muscular rigidity and spasm,[12] so that the muscles are made much looser than before. Normal musculature is unaltered. This release may be enough to convert a hand which was entirely useless into one in which some active, coordinated motion can be accomplished. The movement of picking up a glass of water, holding it and bringing it to the mouth has been taken as a gross typical movement. It means sufficient abduction of the thumb to encompass the glass, flexion and extension of the fingers, supination of the forearm and flexion and extension of the elbow. It is really a complicated maneuver for untrained muscles. If this can be done actively after a single injection of curare, a great deal has been accomplished at one step; if passively, it is still something gained. It must not be forgotten that in addition to plastic muscular rigidity one is dealing with paralyzed muscles, the extent of paralysis of which can be accurately gaged only after release by means of curare therapy.

The patient feels a grateful loosening of the taut muscles. This is confirmed objectively by the greater ease with which active and passive movements opposite to the habitual position of the muscles are carried out. Thus, the thumb can be better abducted, the fingers opened from their flexed position and the hand supinated. Palmar flexion of the wrist is the most difficult to correct, and a certain amount of rigidity remains always in the thenar muscles. Certain groups of muscles, then, are more sensitive than others to the action of curare.

---

10. Rosenblueth, A.; Lindsley, D. B., and Morison, K. S.: A Study of Some Decurarizing Substances, Am. J. Physiol. **115**:53, 1936.

11. Briscoe, G.: The Antagonism Between Curarine and Prostigmin and Its Relation to the Myasthenia Problem, Lancet **1**:469, 1936.

12. It will be noted that no distinction is made between pyramidal and extrapyramidal rigidities of muscle. This distinction is unnecessary since the action of curare is peripheral. The effect of curare on athetoid movements is pointed out elsewhere.

A psychic element plays a part in certain cases of spastic paralysis. There may be a temporary release of rigidity on distraction of attention in happy states or on execution of any procedure believed to be beneficial, such as an injection. In 1 such case the temporary effect of psychic release was well brought out on injection of saline solution, the injection being given in a similar manner (and in similar amount) to that of curare, once with the patient's knowledge and twice without it. The release produced by curare, however, is of much greater intensity and duration.

A soft rigidity will respond better than a more fixed one, and more is to be hoped functionally in the presence of such a soft rigidity. During the regimen of curare therapy there is no return to the original rigidity if the proper overlap effect is maintained.

The reflexes after curare therapy diminish in intensity, and the tendency to clonus lessens. After curare therapy the knee jerk, for instance, may show an active jerk with a dicrotic "step-down" of the descending leg when tap of the patellar tendon gave a sustained or partially sustained clonic effect before administration of curare. In other words, there is an approach to the normal condition. This is also true of the biceps and the radial periosteal reflex.

I had intended making electromyographic study of the action currents of the sound and the paralyzed muscles. I believe this to be not only of theoretic interest but also of prognostic significance. Curare can block only a certain percentage of the nervous impulses coming to the hyperinnervated muscles. If this percentage is relatively constant and if one knows the number of impulses coming to the muscles, it may be possible to estimate accurately the relaxing value of the drug.

Curare therapy should be limited to patients with spasm and plastic muscular rigidity. It abolishes or lessens plastic suspension of a limb and diminishes athetoid movement. It should not be used for patients with fixed deformity.

REPORT OF CASES

CASE 1.—S. E., a boy aged 16 with hemiplegia on the left, weighed 112 pounds (50.8 Kg.). The immediate indication for his admission to the hospital was the operative correction of a marked equinus deformity of the left foot. The hand had never been used. The deformities of the upper extremity were those usual for a spastic arm and hand. A large element of plastic rigidity was present, and it was somewhat difficult to correct passively any of the malpositions of the upper extremity. There was a tremor of the upper extremity, mild when the arm was at the side but definite on attempted use. The boy was intelligent and cooperative.

Small doses of curare were given intramuscularly. Definite loosening of the muscular rigidity took place with doses ranging between 10 and 19 mg. Even a dose of 6.5 mg. gave good release. The highest dose given was 25 mg. There were no subjective symptoms except a slight feeling of sleepiness after a dose of

25 mg. Readings of the pulse rate and the blood pressure before and after each injection indicated no significant change.

For about two days after each injection the hand which had never been used before could open actively, so that the boy picked up a tumbler of water, brought it to his mouth and drank from it. He was able to break an egg with the hand but could not use a knife, fork or spoon. He could take a fountain pen from his pocket and replace it, wind a watch and turn the crank of his bed. The tremor was unaltered. The thumb was still somewhat tight but could be brought away from the hand. Supination was accomplished after the release of muscular rigidity, and flexion and extension of the elbow were easier. The muscles felt much looser, although some element of plastic rigidity remained.

The patient was enthusiastic about the treatment. Since it was believed that a psychic element might play too great a part in his interpretation of the results, he was given injections of physiologic solution of sodium chloride in comparable amounts intramuscularly into the buttock. This was done twice without his suspecting that there had been a change. On the third injection he was informed that he was being given saline solution instead of curare. He noted no such improvement as there had been after the first injection. He made the statement that there was an immediate and good improvement after the second injection, but the next day he regretfully informed me that the effect had not lasted. No improvement was noted after the last injection of saline solution. Psychic release of rigidity is usually transitory; release produced by curare lasts from twenty-four to forty-eight hours. The gait was not tested, since the foot had been operated on before curare therapy was begun and was in a cast.

CASE 2.—L. T., a boy aged 12, had hemiplegia on the right and a mild degree of plastic muscle rigidity. The hand was not used for any useful purpose. The boy could sometimes help himself in dressing. In June 1935 osteotomy of the radius and ulna had been done by Dr. David Telson for the release of pronation contracture of the forearm. The hand was usually held in a neutral position, though sometimes in palmar flexion. The thumb was not drawn into the palm. After administration of 10 mg. of curare intramuscularly the boy was able to use his hand actively. He could write awkwardly with a pencil. Most of the plastic muscular rigidity disappeared.

CASE 3.—T. G., a Negress aged 18, had hemiplegia on the left, of three years' duration. She was syphilitic, and both she and her mother had been treated in the clinic for syphilitic patients for several years. The rigidity of the muscles was extreme. It was almost impossible by strong manual force to secure any supination of the forearm, to extend the fingers or to abduct the thumb. The elbow offered great resistance to extension. The arm was not used for any movement and was maintained in the characteristic, indefatigable position usual to a spastic arm. The reflexes on the left side were greatly increased, with a characteristic tendency to sustained effect. This was especially true of the knee jerk, gentle tapping causing a marked jerk with frequent clonus. The Babinski sign was not present. The reflexes of the (normal) right side were somewhat increased.

Curare therapy effected a relatively amazing release of rigidity. It was, however, never possible to render the arm flaccid. Good release of rigidity was obtained with doses of between 15 and 20 mg. of curare given intramuscularly. The effect of looseness lasted from eighteen to forty-eight hours, and during the period of curare therapy there was no return to the initial rigidity. This was due to an "overlap" effect. After administration of 50 mg. of the drug a greater and more sustained release of rigidity was obtained, which was still manifest at

sixty hours. After administration of 40 mg. the girl was able to flex and extend the elbow actively for a short time. This was the first active movement of the muscles since the onset of her disability. After the dose of 40 mg. she was slightly dizzy for a short time. After administration of 50 mg. she became dizzy and pale, but these symptoms subsided within an hour or so. No effect on the pulse or blood pressure was noted on the occasions when such readings were taken. The reflexes were definitely diminished. The knee jerk expressed itself in a quick kick which subsided gently in two or three dicrotic steps. The biceps and the radial periosteal reflex showed a quick, lively response which was definitely less than before injection. No clonus was noted after injection.

The effect of the curare, which manifested itself in at least one-half hour after intramuscular injection, was greatly accelerated by intravenous injection. The patient had no general symptoms after injection of 10 mg. intravenously. With a dose of 15 mg. an almost immediate release was noted, but she became somewhat dizzy and pale, much as she had been after intramuscular administration of 50 mg.

The thumb could be abducted and the fingers opened passively when the relaxing effect of curare was manifest. Supination could be accomplished almost completely, but at the limits of motion the patient complained of pain because of the stretching of the pronator radii teres. The elbow could be easily extended after an initial rigidity was overcome by slight steady force; passive flexion and extension were then well accomplished. A tumbler could be placed in the loosened hand, and it could be brought to the mouth actively but awkwardly. She was able to hold a pencil in the hand and write an awkward but still legible figure "2" with it. She could accomplish these actions more easily if the sound hand aided the disabled one by opening the fingers and placing the object within them. Correction of the palmar flexion was accomplished with some difficulty.

The duration of the effect of curare was astonishing. It seemed to be present for fifteen days.

The urine was tested once for sugar and showed none.

Case 4.—M. V., a girl aged 13, had spastic paraplegia with a good deal of plastic muscular rigidity. Bilateral hamstring transplants were used to correct the flexion deformities of the knees. The adduction deformity of the thighs was overcome by division of the adductor muscles with resection of the obturator nerves. Both heel cords were shortened because of calcaneus. She was admitted in October 1935 because of bilateral spastic planovalgus deformities of the feet. The feet were rigidly held, so that it was not possible to invert them.

After administration of 20 mg. of curare intramuscularly the plastic muscular rigidity of the lower extremities was overcome in part. The limbs were softer. The feet could be readily manipulated into inversion, the right more easily than the left. The knees were more easily bent. The patient could walk better. The knee jerks were still hyperactive, with some tendency to clonus. There were no general symptoms except a feeling of looseness in the muscles.

Case 5.—Y. N., a girl aged 10, had convulsions at the age of 14 months, followed by paralysis of the right side of the body. She had no use of the right hand and walked with a mild limp on the right. She showed a mild degree of plastic muscular rigidity in the arm and forearm but none in the wrist and hand. The grip of the hand was fair in both palmar flexion and dorsiflexion of the wrist. The fingers were held in neutral position even in palmar flexion. The thumb was drawn into the hand and lay between the middle and the ring finger.

After a dose of 15 mg. of curare was given intramuscularly the hand was very loose, so that the patient could flex the fingers with a fair degree of strength, more than before the administration of curare. She could now use her hand to catch a ball, eat with a spoon, wash dishes and help herself in dressing.

CURARE THERAPY FOR RELIEF OF MUSCLE SPASM AND RIGIDITY IN DYSTONIA MUSCULORUM DEFORMANS

There has been no particularly effective therapy for dystonia musculorum deformans. Putnam [13] sectioned the extrapyramidal tracts by chordotomy in patients with this disease. I am reporting the cases of several patients with this condition who have been treated with curare. The drug has an amazing effect in the reduction of muscle spasm and rigidity, so much so that a bedridden patient may be able to walk. The effect is dramatic and gives a better demonstration of the action of curare than can be obtained in cases of spastic paralysis. Patients with dystonia musculorum deformans tolerate larger doses of curare than those with the ordinary spastic condition, and the average dose, which it is advisable to exceed only cautiously, is in the neighborhood of 25 mg. intravenously. The effect is instantaneous and sometimes maintained for a surprisingly long time, even up to several days. Usually the effect lasts from one to two days, but in some cases only a weekly dose need be given. Symptoms referable to the cranial nerves are not severe and pass away in about half an hour.

The dystonic patient with extreme rigidity may be benefited only slightly. The drug is worthy of a trial, however, even for patients with severe involvement, of which I have had 2. The mechanical situation may be such that even with fair release the patient will not be able to stand.

I have had 2 cases of torticollis resembling spasmodic (dystonic) torticollis, in which the condition seemed to be of psychic origin. In 1 case the patient was cured—if that term is justifiable—by a series of injections of curare. She was a middle-aged woman who had been treated unsuccessfully by other methods for years. When last seen several months after the last injection, she was free from torticollis and spasm. The other case was that of a young man who had severe torticollis of three years' duration. The head was twisted to the right, and the right shoulder was elevated. There was little spasm. He received the largest amount of curare given to any patient, 60 mg. intravenously, and it was only during the fifteen to twenty minute period during which symptoms referable to the central nervous system were present that he was able to correct the torticollis voluntarily and even to twist the head to the left.

13. Putnam, T. J.: Results of Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, Arch. Neurol. & Psychiat. **39**:258 (Feb.) 1938.

The long life of dystonic patients makes some form of therapy imperative.

CASE 6.—V. K., a girl aged 15, was admitted to the hospital on Dec. 19, 1935, and discharged on Jan. 19, 1936. She had had dystonia musculorum deformans for the four and a half years. The most important symptoms were: (1) great difficulty in standing and greater difficulty in walking, neither of which she could accomplish without support; (2) occasional uncontrollable movements; (3) drawing up of the left thigh and hip; (4) difficulty in the finer use of the hands, so that she spilled things frequently and could not write well; and (5) frequently recurring spasm. Even when she was supported by two attendants the patient's gait was difficult and bizarre. Her body was bent to the left (fig. 1) because of a

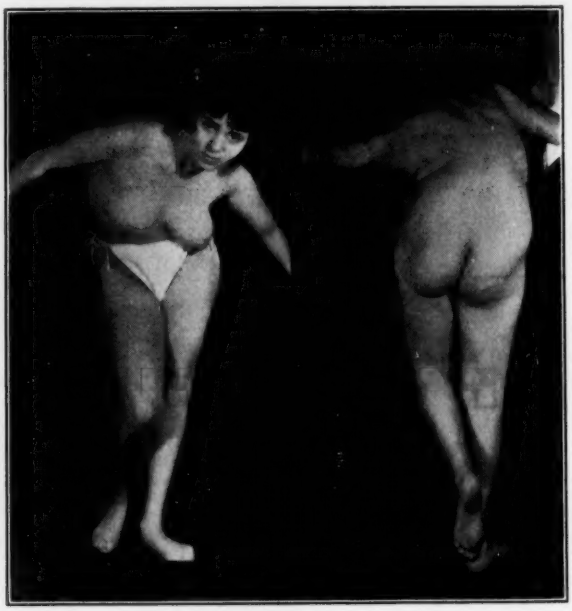

Fig. 1.—General appearance of the patient in case 6 before institution of curare therapy. This photograph shows many of the characteristic deformities but does not indicate the frequency of muscle spasm.

total "C" curve of the entire spine to the right. This condition and pelvic obliquity which elevated the left side of the pelvis almost 2 inches (5 cm.) were due to a spasm of the left lateral abdominal and spinal muscles, especially of the quadratus lumborum muscle. Adduction deformity of the left hip (30 degrees) contributed to the elevation of the left side of the pelvis. Therefore, although the lengths of the lower extremities were actually equal, a great discrepancy in length apparently existed. The upper extremities were also involved, but to a much lesser degree. She had much greater control of the upper than of the lower extremities. Coarse tremors of the hands were seen when the arms were extended. The reflexes of the upper extremities were normal. The cranial nerves were normal. The patient was intelligent.

Curare therapy was begun on Dec. 26, 1935. After the fourth intramuscular injection had been given, a control injection of physiologic solution of sodium chloride was given to rule out any psychic effect. The patient was given 8 cc. of physiologic solution of sodium chloride in the buttock, which corresponded in amount to the volume of solution given in the intramuscular administration of 40 mg. of curare. No objective effect was noted. The patient thought she had a lesser spasm of the left great toe, but otherwise she said she was as restless as before the injection.

The child was given a stabilizing dose of 40 mg. of curare intramuscularly into the buttock or 25 mg. intravenously. The severity of the muscle spasm made her more tolerant to the larger dose than a patient with milder spasm would have been.

The "central" effects were noted about five minutes after intramuscular injection and during or just after intravenous administration. The girl said that her eyes felt heavy, and she had a desire to sleep. A sensation of "fluttering" in front of the eyes was present. Only once did diplopia develop—after an intravenous injection of 25 mg.—and it did not persist for more than twenty minutes. The by-effects were not unpleasant, lasted from one-half to one hour and were relieved by closing the eyes.

The therapeutic effect of curare in effective doses released spasm. The patient noticed a grateful feeling of looseness in the muscles. With repeated doses the spasm tended to return at longer intervals and in lesser intensity. The limbs were looser and showed little rigidity. Within an hour or less after the injection she was able to walk alone, using a cane in her left hand for support (fig. 2). The walking was somewhat awkward, since the body was still bent to the left and the left lower extremity was still elevated because of the pelvic obliquity. She could sit easily. She was able to push the left lower extremity down actively, so as to equalize the length of the legs. She could not sustain this correct position, since a certain amount of tightness presisted in the left lateral muscles of the abdomen and the trunk. She picked up a glass of water (with her right hand) and drank from it, a movement which she had not been able to accomplish for several years. She was able again to write with her right hand.

The effect of curare lasted two days on the average. It was noted that the duration of effect increased with repetition of the dose, so that the last intravenous injection of 25 mg. gave her a relaxing effect which was maintained for at least six days.

Treatments were discontinued on Jan. 29, 1936, when the supply of curare ran out. The girl was readmitted to the Hospital for Joint Diseases early in March. The level of muscle spasm was below that at her original admission, so that she was able to remain still. She was given a dose of 30 mg. of curare intravenously once a week, which appeared to be adequate.

Case 7.—R. S., a girl aged 16, was admitted to the hospital on June 4, 1936. She had had dystonia musculorum deformans since birth. The disease had become progressively worse, so that she had been bedridden for several years. She could not feed or dress herself. Some years previously several operative procedures had been done for the relief of deformity.

She was a well developed, muscular girl. She showed frequently recurring dystonic motions. There was extreme spasticity of the whole body. The left side was somewhat more rigid than the right. The head was held to the left and posteriorly. All the muscles of the neck were taut and elongated, simulating the

appearance of "giraffe neck." The face had a tense look. The right upper extremity was usually in shoulder abduction, elbow flexion, dorsiflexion of the wrist and finger flexion. The limb seemed suspended in air. Plastic muscular rigidity was not so extreme that each joint could not be passively moved through its range of motion. No reflexes appeared. The left hand was sometimes gripped by the right. Plastic muscular rigidity and dystonic movements were greater in the left upper extremity, which was usually held at the side of the body. The patient could not use her hands purposefully. The back presented no constant curvature. Both feet were in calcaneovarus. The deformity could not be corrected manually.

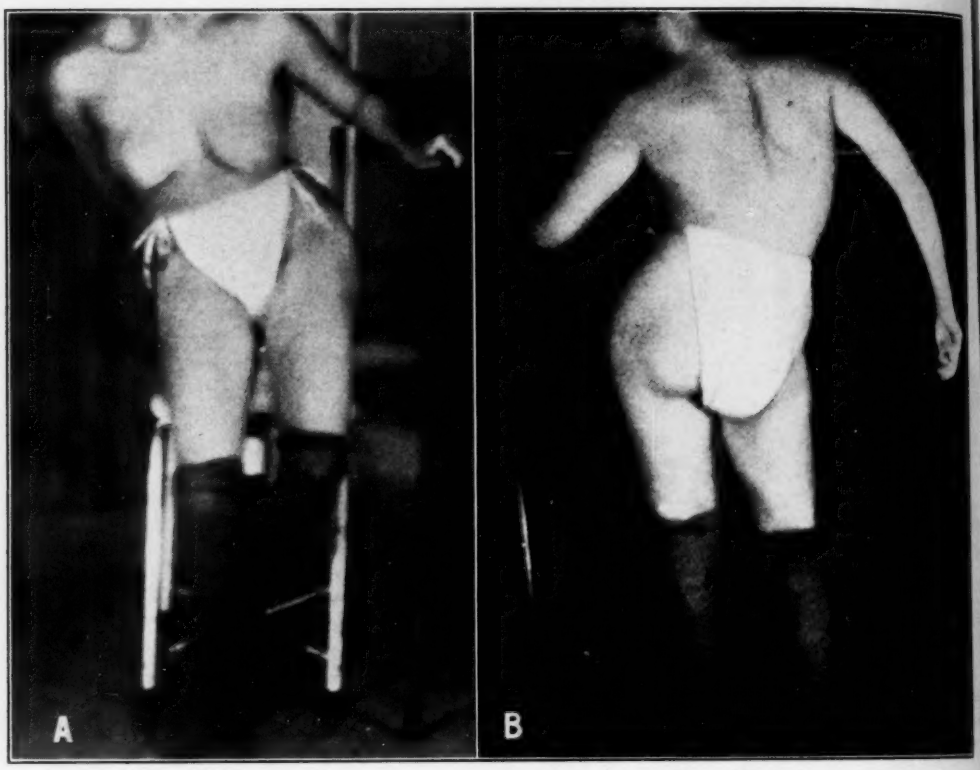

Fig. 2.—Photographs developed from motion picture film. They demonstrate certain phases in the patient's walking after an intravenous injection of 25 mg. of curare. The child walked unaided except by a cane. In photograph *A* she is seen to have risen from the chair on which she was seated and is about to take her first stride. In photograph *B* she is seen to have walked the length of the room by herself. Before the injection, she could walk only if supported. Even then walking was extremely difficult.

The toes were usually flexed and sometimes so bunched together that a pseudo-palm was formed. Occasionally the toes went into the intrinsic positions, and sometimes there was dissociation of extrinsic and intrinsic muscle action of the toes. Both knees were held rigidly in extension, so that passive flexion was impossible. The left lower extremity swung spontaneously upward in hip flexion

and abduction and in knee extension in plastic suspension of the limb. The left side of the pelvis was usually held 1 inch (2.5 cm.) higher than the right. No knee jerks were obtained. The Babinski sign was absent. The patient could not stand or walk. She did not maintain any posture for any length of time, and the movement pattern described was typical. Any simple effort was for her a great, awkward and often futile movement, done with heavy breathing and much sweating.

She was given a stabilizing dose of 25 mg. of curare intravenously. This was effective. She was able to stand in the walker for at least ten minutes and even took a few hesitating steps. She lacked firm pivotal support, since the feet were in varus and the toes bunched up. She was able to feed herself but was not able to write. The spasticity and the plastic suspension of the left lower extremity were greatly diminished. The left lower extremity could be brought down to the level of the bed and stayed there without rebound. She could bend the knees actively, although passive flexion was still most difficult. Sometimes the right lower extremity was looser than the left, and sometimes the reverse was true. The pedal deformity could be passively corrected. The knee jerks came through as quick, hyperactive jerks. The upper extremities were much looser, especially the hands. She became able to grasp a small object, such as a spoon, so that she could feed herself awkwardly. The reduction in rigidity allowed the biceps and the radial periosteal reflex to appear. Dystonic movements were lessened. The head and neck were held quietly, so that they did not tilt. Spastic dysarthria was diminished, so that she was able to articulate much more clearly. She had mild "central" symptoms.

Two cubic centimeters of 1:2,000 (therapeutic) prostigmin was administered subcutaneously soon after the injection of curare. It had no anticurare effect. In the course of therapy urticaria developed. The possibility that it might have been due to sensitization to curare was considered, but further injections of curare gave no allergic effect.

The effect of curare did not last more than from twenty-four to forty-eight hours. Within thirty minutes a degree of rigidity returned, with return of some plastic suspension. The maximum effect of the drug lasted about eight hours. There seemed to be no great overlap effect. The general level of spasm, rigidity and dystonic movements was lower all during the period of treatment.

Case 8.—M. P., a woman aged 22 (from the service of Dr. Harry Finkelstein) had an increasingly progressive tilt of the head, which followed a severe grippal infection in April, 1935. She had dystonic torticollis which drew the head and neck to the right. This deformity persisted, but was sometimes relaxed in sleep. No definite tremor was present. There was a definite spasm of the right trapezius muscle. Scoliosis of the cervical portion of the spine to the right, with the apex at the level of the third cervical vertebra, was seen. Roentgenographically there was a distinct upward subluxation of the second cervical vertebra on the right. Associated movements of the left arm were diminished. The deep reflexes were active. The Babinski sign was absent. A diagnosis of dystonic syndrome following epidemic encephalitis was made by the neurologist.

Motions of the cervical portion of the spine were tested before curare was given. Right lateral bending of the neck was possible passively, so that the tip of the ear and the shoulder were 3½ inches (8.8 cm.) apart; actively, 5½ inches (13.9 cm.) apart. Left lateral bending was free, so that the left ear touched the left shoulder. Rotation of the neck to the right brought the face around 45 degrees, while rotation to the left did so to 90 degrees. Flexion and extension of the neck

were complete. Limitation of motion was conditioned not only by increased spasticity of the cervical muscles, especially the right trapezius, but also by the bony deformity, an upward subluxation of the second on the third cervical vertebra resulting from spastic cervical scoliosis. Pressure against the convexity of the curve, that is, from right to left, corrected the scoliosis to some extent.

The patient was given a stabilizing dose of 50 mg. of curare intramuscularly. She was given no intravenous injections. She showed mild symptoms referable to the cranial nerves. The head and neck felt looser, and the dystonic position of the head was easily corrected. The head could now be bent completely to the right by active movement, so that the right ear touched the right shoulder. Passively some bony resistance was felt on lateral bending to the right, but this was quickly overcome, and the head then moved easily. This was noted when the patient performed this movement herself as a peculiar movement of the neck. Apparently, at this point in motion the subluxation of the neck was reduced. This was confirmed by roentgenograms, which showed reduction of the subluxation in the position of lateral bending to the right after administration of curare. The subluxation was present in lateral bending to the right before administration of curare. The head was held in a normal line after curare was given. Spasticity of the cervical muscles was greatly lessened. Rotation to the right was increased to 60 degrees. The scoliosis (curvature of the cervical portion of the spine to the right and of the dorsal portion to the left) was diminished.

The effect of the curare lasted about four hours. The patient received treatment only during her stay in the hospital, movement taking place as a result of overlap effect. She was seen last in September 1936. The position of the neck and head was good, and the muscles had felt loose for several months. The patient was in a state of remission from spasm and was given no further treatment.

Case 9.—H. D., a youth aged 19, presented a fractional dystonic syndrome, the main expression of which was spasmodic torticollis. His illness had begun at the age of 5 years and had gradually become worse. He had slowness of speech, which developed after the onset of the disease. A year before admission he was operated on at another hospital, where resection of the right eleventh cranial nerve was done. This operation was unsuccessful and caused a distressing droop of the right shoulder.

The boy was intelligent and ambitious; he was keenly interested in sports and wished to become a sports writer. The head was held to the right about 25 degrees, the chin pointing to the elevated left shoulder. There were a constant gross spastic nodding and finer tremor of the head and neck muscles. As the boy walked, the left shoulder was elevated 2 inches (5 cm.), and there was compensatory scoliosis, the dorsal portion of the spine being curved to the left and the lumbar portion to the right.

Tremor and spasm of the right upper extremity, shoulder, neck and scapular muscles were fairly marked even with the patient at rest. Spasm was most marked in the right trapezius muscles but was widespread enough to include all the scapular muscles. The right shoulder moved up and down in a jerking motion as the boy stood. He could write with both hands, but writing with the right hand increased the extent of the spasm. His writing was jerky, irregular and spasmodic, but it could be read.

He was given a stabilizing dose of between 22 and 25 mg. of curare intravenously. This dose reduced the spasm almost completely, although a fine tremor of the head could still be seen. The head was easily held straight. The spasm of the neck and shoulder muscles was so reduced that even on violent exercise, such as

shadow boxing, only an occasional spasmodic contraction of the trapezius muscle was seen. The handwriting improved greatly, but writing still produced a greater extent of spasm than did exercise. The reduction in spasm was accompanied by mild to moderate symptoms referable to the cranial nerves; these passed away quickly.

After a dose of 32 mg. of curare given intravenously there was an alarming display of symptoms. The patient's face became grayish and pale. His expression was fixed in amazement. He could not stand or walk, because of ataxia. The lower extremities felt weak. Saliva drooled from his mouth. He was extremely

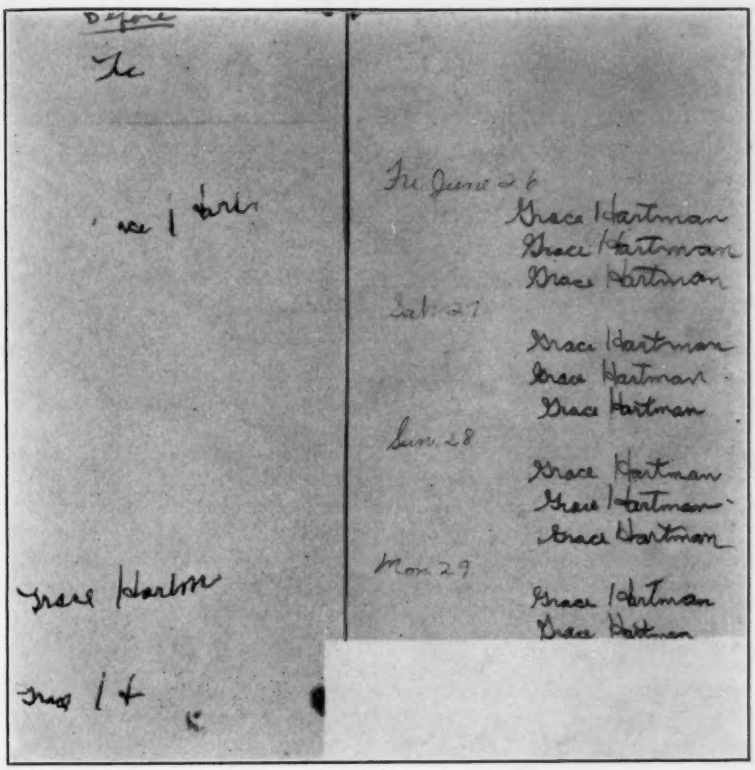

Fig. 3.—Specimens of the handwriting of a dystonic patient before (left) and after (right) curare therapy. The specimen taken before treatment indicates inability to write her name completely and clearly. This has been done in the specimen on the right.

dizzy; his eyes were heavy, and he kept the lids half closed. He "saw double." He had a gripping sensation in the throat. There was no spasm. The head was heavy and limp and had to be supported. The patient was put to bed, and symptoms disappeared in from five to ten minutes. No immediate danger to life was feared, for the pulse was regular and the breathing undisturbed. (This dose of curare is larger and the result illustrates the mathematical exactness of response to curare. These symptoms were not produced by a proper effective dose.)

Curare gave him relief of spasm for a week. He demonstrated a good overlap effect, and there was no return to the original level of spasm. At the time of this report the dose has been reduced so that he gets along well with 20 mg. intramuscularly or 10 mg. intravenously, with complete absence of "central" symptoms.

ERYTHROIDINE

Since it has been so difficult to obtain and standardize large quantities of curare for clinical use, I have tried erythroidine. This drug is mentioned in the United States Dispensary as a powerful motor paralyzant. It is derived from the seeds of the species Erythrina coralloides and was isolated by Altamirano [14] in 1888. (See also Folkers and Major.[14])

The erythroidine which I used was put up in sterile ampules. The strength of the preparation varied somewhat with different lots; tests on animals showed it to be far lower both in toxicity and in effectiveness than curare.

So far, I have given erythroidine intravenously in 5 cases, but in only 2 has a therapeutic effect been obtained, owing to the small quantities of the material available. The following case will illustrate its effect.

CASE 10.—A girl aged 15, who weighed 118 pounds (53.5 Kg.), had dystonic hemiplegia on the right. The right arm showed coarse, large and frequent upward and downward movements. The fingers showed frequent intense spasm and dissociated action of the extrinsic and intrinsic muscles of the hand. One finger might be held in the intrinsic position; the finger next to it might be in the extrinsic position. There was also a good deal of muscular rigidity. The patient had been given 45 mg. of curare intravenously, without effect. The highest dose of erythroidine hydrochloride she had received was 950 mg. intravenously, with good reduction in muscular rigidity and spasm. Release of rigidity began on administration of about 300 mg.

Transient and slight dizziness was noted by the patient even after a small dose. As the dose was increased the dizziness might increase, but it was never as intense as after administration of curare. A peculiar circumoral pallor with frontal and buccal flush was always seen, even after ineffective doses. Heaviness of the upper eyelids, which became a transient palsy, was noted after larger doses. The eyes remained half closed. After the largest doses given the eyes were closed and the patient could not elevate the upper lids. The partial palsy of the upper lid began on administration of about 280 mg. It lasted only a few minutes. The drooping of the upper lids was also noted after administration of curare, but it was more clearcut after administration of erythroidine. Diplopia and slight nystagmus were present after a dose of 480 mg. Movements of the eyes were slowed by very large doses but were not abolished. The blood pressure was unchanged, as was the pulse rate. The urine showed a persistent trace of albumin, even in a catheterized specimen, but this did not seem to be due to the

14. Altamirano, F.: Nuevas apuntas para el estudio del coralin—erytrina coralloides, Gac. méd. de México **23**:369, 1888. Folkers, K., and Major, R. T.: Isolation of Erythroidine, an Alkaloid of Curare Action, from Erythrina Americana Mill., J. Am. Chem. Soc. **59**:1580, 1937.

erythroidine. Abnormal motor movements, spasm and muscular rigidity were greatly diminished, and this was most marked in the first fifteen minutes after the injection. The effect of the drug did not last more than twenty-four hours, as judged by the patient's own observation. No ataxia, salivation or flaccidity of the cervical muscles was observed. There was never any respiratory difficulty.

Erythroidine must be given in larger doses than curare and in even greater doses than its experimental assay indicates. It has a definite curare-like effect which should make it valuable. The order of symptoms produced by it is like that of symptoms caused by curare, the cranial nerves first being affected and then the motor system. It seems to be safer than curare and to have a wider range of safety. It has the advantage over the latter that it can be easily made up and accurately assayed.

This report is preliminary. The work will be carried on as more of the drug becomes available.

CONCLUSION

Properly assayed curare is safe if given in therapeutically effective doses. It has a definite place in the release of spasm and plastic muscular rigidity in patients with spastic paralysis. It produces its effect by an elective affinity for the hyperinnervated myoneural junction. This work is confirmed clinically and experimentally. The drug cannot be casually used, and each patient needs careful watching.

The release of spasm and plastic rigidity is only one phase of the treatment of spastic paralysis. It cannot be expected that the drug should convert a paralyzed muscle into an active one. In certain cases the release of rigidity may allow a muscle not completely paralyzed to begin functioning actively. Simple orthopedic operations and continuous training of the muscles must be used in conjunction with curare.

The plight of spastic and dystonic patients is worse than that of patients with infantile paralysis. Curare can help them to some extent.

Merck & Co. supplied the curare and erythroidine used in this study. My chief, Dr. Leo Mayer, encouraged me in this work and allowed me to report cases observed in his service. Dr. Harry Gold, of the department of pharmacology of the Cornell University Medical School, gave advice during the study, and Dr. A. M. Gold assisted me in the early part of the investigation.

DISCUSSION

DR. WALTER FREEMAN, Washington, D. C.: I think that every one who has studied the results of curare and has observed cases of hypertonus has wondered if something cannot be found to weaken the muscles sufficiently to make the hypertonus disappear. About fifteen years ago, while working in Paris, I tried curare in a few cases, but probably in doses insufficient to produce results. Many physicians were using extract of hemlock, but with mediocre results.

DR. ROBERT B. OSGOOD: Much in these cases is not evident from the history. They constitute a vast problem which belongs both to the neurologist and to the

surgeon. From the orthopedic point of view, the attack was unsatisfactory before the work by Dr. Burman.

DR. PAUL F. A. HOEFER: I congratulate Dr. Burman on his presentation and on his courage. I regard curare as a dangerous drug. My colleagues and I have tried it successfully in some cases and, like Dr. Burman, have tried some of the substitutes, with little result. The decrease has not occurred in the number of impulses but only in their amplitude, though, from Bremer's studies on decerebrate rigidity, one would expect the first effect. An observation I made several years ago seems important. I found, in a reflex preparation, that both the ipsilateral and the contralateral nerve impulses for a defense reflex were abolished by curare.

DR. TRACY J. PUTNAM: I have been amazed to observe the fact which Dr. Burman has brought out, as far as I know for the first time, that the effects of curare are lasting in man beyond those observed in animals. While treatment of this type is impractical at present, the fact that gratifying relief can be obtained holds out the hope that more may be accomplished in the future. There is no question that different samples of the drug vary in duration of effects. In my experience there have been no lasting effects with the erythroidine group.

DR. HALLOWELL DAVIS: Curare, in spite of its known dangers, is now available for clinical use through standardization. It can be used perhaps with less fear. Success with it is another question. How long do the benefits last after one injection? For how many lasting effects can one look from curare?

DR. ARTURO ROSENBLUETH: I wish to ask Dr. Burman whether he has given curare to normal persons and, if so, what were the effects. Curare is capable of modifying autonomic reflexes and responses. The effects of curare are partly central, not alone peripheral. The field of study of the effects of curare on the central nervous system is wide open.

DR. M. S. BURMAN: With regard to the questions concerning the use of curare and substitutes, it should be noted that not all these drugs must be given by intravenous injection. Erythroidine hydrochloride may have an effect by mouth, but has had none, even up to 3,000 mg. A patient who needs lifelong attention cannot be allowed to administer the drug to himself. The use of insulin is comparable with that of curare. The effects of insulin are better known, and hypoglycemia is easy to treat. Asphyxia produced by curare is serious, especially if the curare has been administered by the patient. The danger of the drug is only potential, if used carefully. One should always start with a small dose and increase until a stabilizing dose is reached. If it is continued for a long time, there will be an overlapping effect, and it does not need to be given so frequently. One patient was able to remain for two weeks without curare and did not return to the original state of abnormal movements. I have no explanation for this.

As regards Dr. Hoefer's point about the danger of curare, the drug is powerful and dangerous, but if used in the proper dose is a friend; if not, it is an enemy. If one observes the patient's face as the curare is given, one has a reliable index as to how much of the drug has been given. One can guess the dose without knowing how much curare is in the syringe by the expression on the patient's face, by seeing the smoothing out of the facial muscles and the palsy of the upper lid.

In reply to Dr. Rosenblueth's question concerning the dose of curare for normal persons, I have not yet tried it, for no one has been willing to submit himself as a patient, but I know that the dose used in patients with spastic conditions might prove fatal in normal persons. Hyperinnervated muscles need larger doses of the drug.

As regards the difference between central and peripheral effects: I am not a pharmacologist. Peripheral effects are effects which are confined to the extremities and the spine; central effects are those confined to the neck and above.

Certain effects cannot be explained in such terms as dizziness. I do not know what the mist in front of the eyes means. I must admit that I do not know all about the drug, but when I give it I expect certain effects, both motor and central. Of course, that does not tell the whole story.

With regard to the lasting effects of curare: It must be given over a long period. I have no case in which I have continued treatment for over one year. My observations were checked by the hospital staff. My findings were always submitted to this group and always agreed with theirs, so that I feel that I was not deluded.

LYMPHOMATOID DISEASES INVOLVING THE SPINAL EPIDURAL SPACE

A PATHOLOGIC AND THERAPEUTIC CONSIDERATION

JEFFERSON BROWDER, M.D.
AND
J. ARNOLD DE VEER, M.D.
BROOKLYN

An extensive literature has accumulated concerning the diagnosis and treatment of benign tumors that occur within the vertebral canal. Monographs, chapters in textbooks and many excellent articles on this subject indicate the clinical course of these lesions and the favorable outlook as to life and function following their surgical treatment. A second group of tumors, namely, the primary growths of the spinal cord itself, has been given considerable attention in recent years, particularly with regard to histogenesis.

In striking contrast to the voluminous literature dealing with the benign extramedullary and the usually malignant intramedullary tumors of the spinal cord there is a paucity of information concerning other malignant lesions observed within the vertebral canal. We refer to the malignant neoplastic processes that invade the spinal epidural space and frequently produce compression of the spinal cord. As examples of such lesions, we have encountered Hodgkin's disease, myeloma, carcinoma and several types of lymphosarcoma. Although implication of the spinal epidural space in these diseases has been generally regarded as an index of widespread involvement by the malignant growth the records of our series of tumors of the spinal cord reveal 16 cases of malignant epidural tumors in each of which the initial observations indicated compression of the spinal cord or cauda equina. The malignant character of the process, in every instance, was suggested only by the relatively rapid progression of the symptoms and signs. Roentgenographic and other examinations failed to disclose any evidence that the lesion within the vertebral canal was not primary in that location. The true nature of the tumor was disclosed by surgical exploration, histologic examination of the excised tissue and subsequent clinical developments. There were in this group 4 cases of carcinoma. The remaining 12 cases had been classi-

---

Read at a meeting of the Brooklyn Neurological Society, Oct. 27, 1937.

From the Division of Neurosurgery and the Department of Pathology of the Brooklyn Hospital.

fied under the designation lymphoblastoma, for which Krumbhaar [1] has recently suggested the name lymphomatoid diseases.[2] A recent review of these cases has resulted in the following classification: lymphosarcoma, of which there were 8 examples, and giant follicular lymphadenoma, reticulum cell sarcoma, plasma cell myeloma [3] and Hodgkin's disease, of which there was 1 case each. Our attention was attracted to this group in particular because of the long period of survival of 2 patients whose infiltrating spinal epidural tumors were diagnosed as giant follicular lymphoblastoma and lymphosarcoma, respectively. The 12 cases have been analyzed and the records of 6 have been incorporated in this presentation to illustrate the distinctive clinical and histologic features encountered.

REPORT OF CASES

CASE 1.—*Pain in the upper part of the spine, radiating around the midthorax; four months later, weakness and numbness of the lower extremities; progressive loss of function of the legs; occasional urinary incontinence. Bedridden for three months prior to operation. Laminectomy. Giant follicular lymphadenoma. Roentgenotherapy. Gradual recovery. Well four and one-half years after operation.*

M. G., a woman aged 37, was admitted to the hospital on March 25, 1933, complaining of "paralysis from the waist down." She had been well until April 1932, when there occurred electric-like shocks arising between the shoulder blades and radiating around the upper left side of the thorax posteriorly. The transitory pains continued until early in June 1932, when there developed a dull ache in the upper part of the back. About one week later there was an occasional sharp, shooting pain around the midthorax on either side. Slowly the pain in the back became more severe and the radiating pains more frequent. Jarring, coughing or sneezing aggravated the condition considerably. In August 1932 the left leg and foot felt numb, and the right lower extremity became stiff. The spasticity of the right lower extremity increased, and in the early part of September 1932 the left lower extremity began to show similar involvement. From this time until December 1932 walking was increasingly difficult, and eventually the patient was compelled to remain in bed. Occasionally, urinary control was lost for a day, but continued incontinence had not been present. No voluntary motion was present in the right lower extremity for one month prior to entrance to the hospital; however, motion of the toes was retained on the left side.

Examination.—The patient was well nourished and did not appear ill. The head, cranial nerves, neck and upper extremities showed no demonstrable abnormalities. Moderate tenderness to percussion was present over the upper thoracic portion

1. Krumbhaar, E. B.: The Lymphomatoid Diseases (So-Called Lymphoblastomas), J. A. M. A. **106**:286 (Jan. 25) 1936.

2. Under this convenient designation Krumbhaar included lymphatic leukemia, lymphosarcoma, reticulum cell sarcoma, aleukemic reticulosis, leukosarcoma, Hodgkin's disease, granuloma (mycosis) fungoides, Mikulicz's disease and the diagnostically related diseases myelogenous leukemia, monoblastic and monocytic leukemias, agranulocytosis, Cooley's erythroblastic anemia, infectious hemolytic anemia, hepatic thrombosis and von Jaksch's disease.

3. We believe that the myelomas should be added to this group.

of the spine. Support was necessary when the patient attempted to sit erect. The abdominal muscles were relaxed, and the abdominal reflexes were not obtained. The spleen was not palpable. The lower extremities were mildly atrophic and lay fully extended and rotated externally. Neither the thighs nor the legs could be flexed or extended voluntarily. The toes of the left foot could be actively flexed and extended, but on the right side only the foot could be voluntarily moved, and that through a small arc. Hyperreflexia, ankle clonus and the Babinski sign were demonstrable in both lower extremities. Perception of position and vibratory stimuli (128 double vibrations) was not present in the involved extremities. Appreciation of touch was present over the hairy parts, but was markedly diminished over the other cutaneous surfaces of the feet, legs and thighs. Sensations of pinprick and thermal stimuli were diminished approximately 50 per cent in the lower extremities and over the buttocks and the lower part of the abdomen. From here to the cutaneous area supplied by the sixth thoracic nerves there was a gradation in the direction of normal. A definite level could be established at the sixth thoracic dermatome. The urinary bladder was not distended. The external anal sphincter could be voluntarily contracted. Examination of the blood showed 3,600,000 red and 4,100 white cells per cubic millimeter. The hemoglobin was 84 per cent (Sahli). No abnormal white cells were found. The results of urinalysis, the nitrogen and sugar contents of the blood and the Wassermann reactions of the blood and spinal fluid were normal. Spinal puncture in the third lumbar interspace disclosed xanthochromic fluid, and a block of the spinal subarachnoid space was demonstrable by jugular compression. Roentgenographic examination of the vertebral column showed that the left articular facets of the third, fourth, fifth and sixth thoracic vertebrae were less distinct than the corresponding facets on the right side.

Operation.—On April 3 laminectomy of the third, fourth, fifth and sixth thoracic vertebrae was performed. A tough, grayish pink epidural tumor, extending from the level of the midpart of the third thoracic vertebra to the lower part of the fifth thoracic vertebra, was observed. At either end the tumor tissue blended with the epidural fat, and the mass extended laterally as far as could be visualized. The tumor was easily separated from the dura, which was not grossly invaded. The strip of tumor which presented in the laminectomy opening was removed. The dura was incised, and no tumor tissue was seen in the subdural space. The wound was closed with silk.

Histologic Examination.—There was extensive replacement of the normal adipose and areolar structures by a new growth, consisting of insular aggregations of lymphocytic cells, each group containing large, sharply demarcated germinal centers. Between the germinal centers were closely packed small lymphocytes. These islands simulated the structure of normal lymph nodes, but were not encapsulated. The lymphoid cells at their margins invaded the adjacent adipose tissue (fig. 1). Active growth was indicated by numerous mitotic figures in the cells of the germinal centers. The infiltrating lymphocytic cells were of uniformly small size and showed rare mitosis.

Course.—The wound healed primarily, and the patient was allowed out of bed on the fourteenth day after operation. She was able to walk with assistance one month from the date of operation. Roentgenotherapy was instituted. During six weeks a total dose of 4,242 roentgen units, centered over the operative wound, was given. Repeated examinations in the course of the ensuing year showed progressive improvement in gait and reestablishment of normal cutaneous sensation. Yearly examinations have disclosed mild hyperreflexia and a slight degree of spasticity of the right lower extremity.

Repeated examination of the blood has failed to show any abnormality of the white cells. The patient was delivered of a normal child in May 1937 and at present is apparently in good health.

The relatively slow development of the symptoms and signs in this case suggested that the tumor might be benign, and it was with considerable surprise that an ill defined and seemingly malignant growth was uncovered at operation. Complete removal of the tumor was impossible, but the portion excised served to relieve the compression of the spinal cord. The histologic observations were in accord with the history and the gross anatomic observation. The tumor was of the type described in recent literature as giant follicular lymphadenoma, a variety of lymphosarcoma. The combined effects of the decompression and irradiation resulted in satisfactory recovery. As is evident from the amount of radiation recorded, this form of treatment was carried to the limit of tolerance. Considering the amount of tumor tissue left in the vertebral canal and the failure of symptoms to recur during the past four and one-half years, one may reasonably conclude that the new growth at this site has been destroyed.

CASE 2.—*Pain in the lumbar region, radiating into the right hip and groin. Orthopedic operation. Apparent temporary improvement. Progressive loss of power in the lower extremities; urinary retention. Laminectomy. Lymphosarcoma. Roentgenotherapy. Improvement. Living and without residual symptoms two and one-half years after operation.*

H. H., a man aged 50, was admitted to the hospital on April 22, 1935, complaining of pain in the lumbar region, which at times radiated into the right hip and groin. He had been in good health and had worked until the middle of February 1935, when a dull, aching pain in the upper lumbar region was noticed. Gradually, the pain became constant and more severe, at times radiating into the right hip and groin. Walking aggravated the pain, and the radiations were especially prominent when he was jarred, as in stepping from a curbstone. One month after onset he noticed that sitting was the most comfortable position. He was compelled to give up work, and from the middle of March 1935 until entrance to the hospital many palliative medicinal and mechanical measures were employed, without relief from pain.

Examination.—The patient was well nourished and cooperative, in obvious discomfort and unable to extend the right lower extremity fully without increasing the pain in the back and right thigh. The head, cranial nerves and upper extremities presented no significant abnormalities. No enlarged lymph nodes were palpable in the neck, axillas or groins. The abdominal and cremasteric reflexes were equally active on the two sides. There was tenderness on percussion of the posterior spinous processes of all lumbar vertebrae, and the lumbar portion of the spine was held in a fixed position by muscular spasticity. The right lower extremity was voluntarily held slightly flexed, since motion of the leg or thigh aggravated the pain in the back. The knee, hamstring and ankle jerks were brisk, but equal bilaterally. Poorly sustained ankle clonus was demonstrable. Plantar stimulation produced a flexor type of response. In walking the patient carried the trunk forward and limped, favoring the right side. There were no evident disturbances

of cutaneous sensations. The sphincters (anal and vesicular) functioned normally. Laboratory studies showed nothing abnormal. Roentgenographic examination of the lumbar portion of the spine and pelvis disclosed a bony growth projecting from the left superior articular process of the fifth lumbar vertebra.

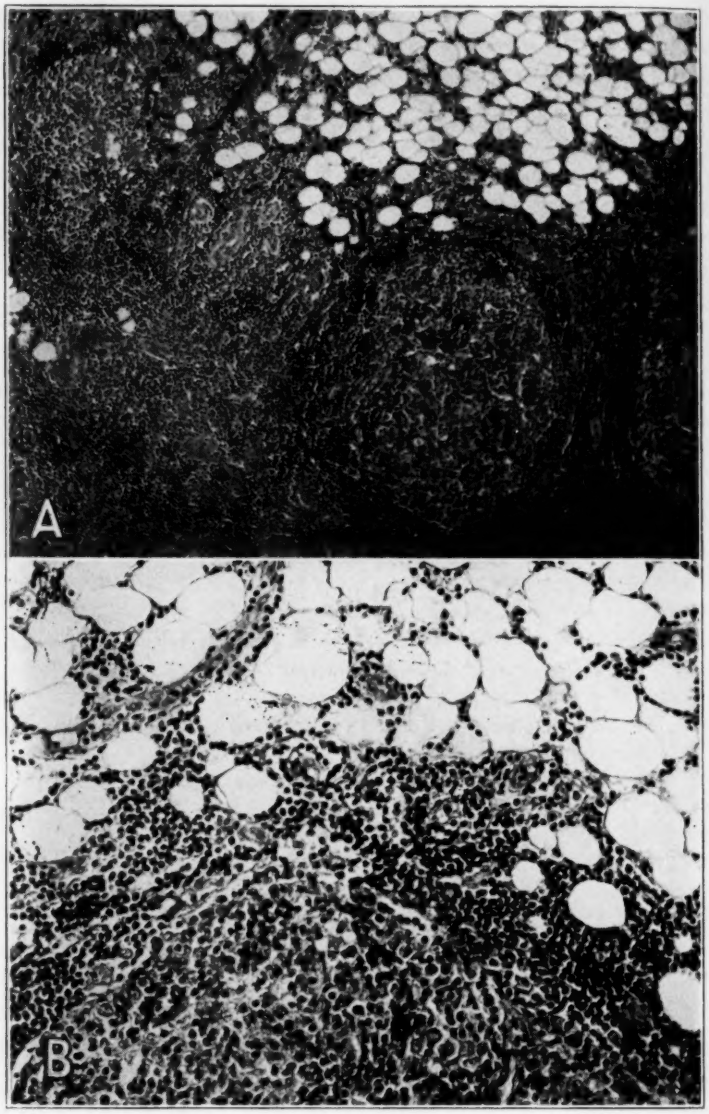

Fig. 1.—Tissue from the epidural space in case 1, showing the large germinal centers surrounded by densely packed lymphocytes. The picture resembles that of benign lymphoid hyperplasia. Infiltration of the normal adipose tissue by tumor cells is shown in the upper portion of each field.

Operation.—On April 23 an unsuccessful surgical attempt was made to expose the abnormal area of bone. A portion of a bifid spinous process of the fifth lumbar vertebra was removed. Histologic examination of this specimen showed normal bone.

Course.—After recovery from this operation a plaster of paris jacket was applied on May 7, and the patient was discharged from the hospital on the following day. For the next two weeks he was comfortable, but at the end of this time the pain in the back returned and now radiated into the region of the groins and the anterior aspect of the thighs. When he was readmitted to the hospital on May 24 the urinary bladder was distended; according to the patient's statement, catheterization had been necessary on the previous day. In addition, there was moderate weakness of the lower extremities, which was about the same on each side. The

Fig. 2 (case 2).—Roentgenogram taken after the subarachnoid injection of iodized poppyseed oil, showing arrest of the descending contrast medium at the upper part of the eleventh thoracic vertebra.

gait was ataxic, and there was inability to walk on the toes or the heels. The left knee jerk was obtained, but the right knee and ankle jerks were not demonstrable. There were hypalgesia and hypesthesia over the posterior aspect of the thighs, the buttocks and the lateral aspect of the legs. The exact extent of this cutaneous disturbance could not be outlined. Coughing caused sharp pains to shoot into the left groin. Routine laboratory examinations disclosed nothing abnormal. Spinal puncture in the second lumbar vertebral interspace showed xanthochromic fluid, and a block of the spinal subarachnoid space was demonstrated by jugular compression. The total protein content of the spinal fluid was 345 mg. per hundred cubic centimeters. Withdrawal of the spinal fluid was followed by severe pain in the left groin, which persisted for several hours. On May 29, 0.5 cc. of iodized poppyseed oil was introduced into the spinal subarachnoid space by the cisterna

magna route. Subsequent roentgenographic examination revealed almost complete subarachnoid block at the upper level of the eleventh thoracic vertebra (fig. 2). A second examination of the vertebral column from the eleventh thoracic to the second lumbar vertebra failed to disclose evidence of changes in the bone.

Second Operation.—On June 1 laminectomy of the eleventh and twelfth thoracic and the first and second lumbar vertebrae was performed. On exposing the vertebral canal a firm, grayish pink mass was seen extending from the level of the inferior margin of the eleventh thoracic to the superior margin of the second lumbar vertebra. The dura was "unroofed" by removing a strip of tumor, 1.5 cm. in width. The laterally placed tumor tissue was not disturbed, but the roots of the right first lumbar nerve, which passed through it, were crushed intradurally.

Histologic Examination.—Microscopic examination of the tissue revealed a malignant tumor composed of lymphoblastic cells occurring in broad sheets in a delicate reticulum (fig. 3 *A*). Two predominant cell types were distinguishable: one a large cell, resembling those in the germinal centers of a normal lymph node; the other a smaller cell with the appearance of an adult lymphocyte. The former were arranged in ill defined groups and showed marked anaplasia. In the intervening tissue cells of the more adult type predominated. Extensive areas of necrosis were present.

Course.—The postoperative course was uneventful. The patient was able to void voluntarily on the sixth day after operation and was allowed out of bed on the twelfth postoperative day. Motor power in the lower extremities gradually improved, and he was discharged from the hospital on June 5. During July and August 1935 radiation therapy was instituted over the operative field only, and in twenty-eight consecutive treatments a total dose of 4,412 roentgen units was given. Repeated physical examinations have failed to show extension of the disease, and there has been no evidence of local recurrence.

It was strongly suspected prior to operation that this patient had a malignant tumor in the vertebral canal, although no primary focus could be identified clincally. The appearance of the tumor at operation was in no respect different from the lesion in case 1, but histologic examination indicated that it was of more embryonic type. No discrete germinal centers were present, but poorly delineated islands of lymphoblastic cells were interpreted as analogous structures. A maximum amount of roentgenotherapy was given to the tumor area, and the period of survival, with absence of local recurrence or evidence of the disease elsewhere, has been far beyond expectation.

CASE 3.—*Pain in the back; progressive weakness and stiffness of the legs; retention of urine; sensory level at the sixth thoracic dermatome. Laminectomy. Lymphosarcoma. Inadequate roentgenotherapy. Six weeks after operation palpable lymph nodes in the left axilla. Lymph node removed surgically showed lymphosarcoma. Enlargement of liver; masses in abdomen; jaundice; ascites. Death.*

J. F., a man aged 27, was admitted to the hospital on Aug. 11, 1933, complaining of pain in the upper part of the back and weakness of the legs. He had been in good health until the early part of June 1933, when he noted pain in the left upper part of the thorax posteriorly and intermittent pain in the right shoulder. Local application of a liniment was followed by complete relief. Ten days later a dull ache appeared in the midpart of the back and became progressively worse.

At this time the hips and thighs were sore. The discomfort in the back continued throughout July, but at no time was there associated radicular pain. During the early part of August the legs felt "heavy," and the gait became unsteady. From then until his entrance to the hospital, weakness of the lower extremities had been noticeable, and the patient had begun to experience difficulty in starting the stream of urine.

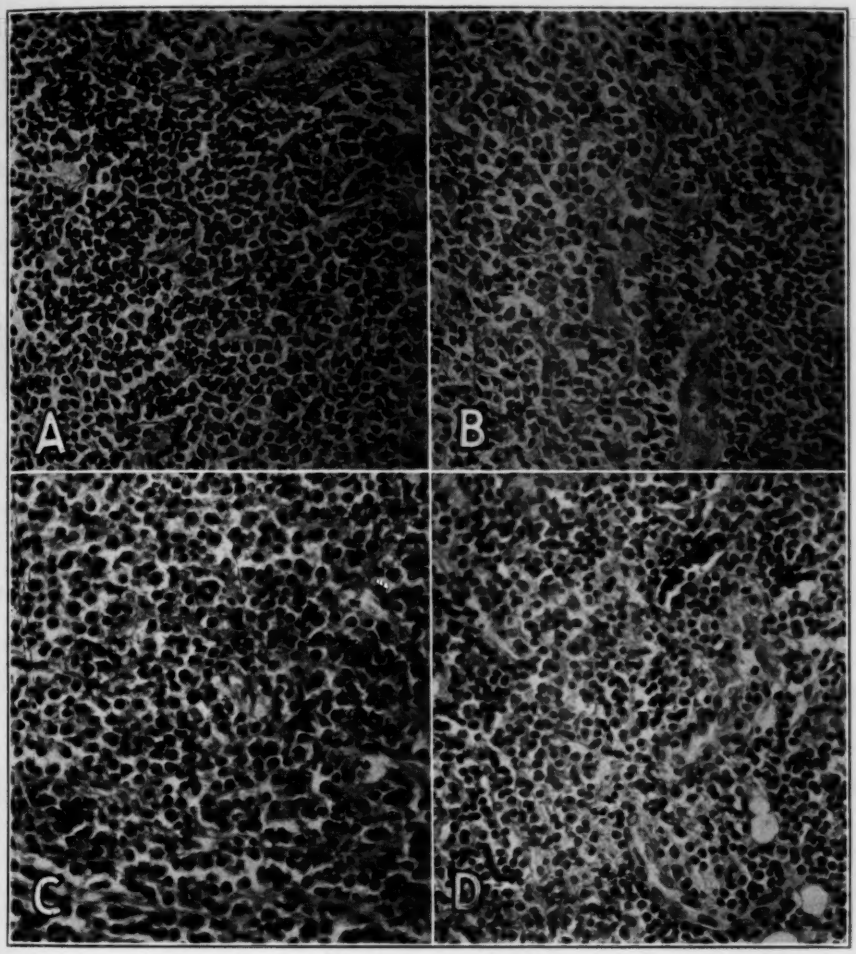

Fig. 3.—Representative microscopic fields in cases 2, 3, 4 and 5. There is considerable similarity of the various lesions. In *A* (case 2) the cell type is the small lymphocyte. The tumor shown in *B* (case 3) is considered a reticulum cell sarcoma. In *C* (case 4) large lymphoblastic cells predominate. Mitotic figures are numerous throughout the tissue. The tumor shown in *D* (case 5) is interpreted as Hodgkin's disease. A variety of leukocytes are present, including many eosinophils, but they cannot be readily identified in the photograph. There are rather marked vascularity and some hyperplasia of reticulum cells.

Examination.—The patient was pale but well nourished and could not stand alone. There were no palpably enlarged lymph nodes in the neck, axillas or groins. Examination of the head, neck and upper extremities showed nothing abnormal. There was tenderness over the posterior spinous processes of the sixth and seventh thoracic vertebrae. Caudad to the cutaneous area supplied by the sixth thoracic spinal nerves, appreciation of painful and thermal stimuli was markedly diminished. Appreciation of touch and vibratory stimuli was not grossly disturbed over the lower part of the trunk and lower extremities. The abdominal and cremasteric reflexes were not elicited. The deep reflexes of the lower extremities were present, but were not considered to be abnormally active. A Babinski sign was demonstrable bilaterally. Marked weakness of the lower extremities was present. The urinary bladder was not distended. Examination of the blood showed 4,100,000 red and 7,200 white cells per cubic millimeter, and the hemoglobin was 75 per cent. No abnormal white cells were found. Urinalysis gave normal results. The Wassermann reactions of the blood and spinal fluid were negative. Spinal puncture at the third lumbar vertebral interspace disclosed xanthochromic fluid, and a block of the subarachnoid space was demonstrable by jugular compression. Roentgenographic examination of the vertebral column and the thorax disclosed nothing abnormal. Urinary retention was present on the day after spinal puncture. The urinary bladder could not be emptied by manual expression, and catheterization was resorted to.

Operation.—On August 21 laminectomy from the fifth to the eighth thoracic vertebrae was performed. A grayish blue epidural tumor was seen to extend from the lower border of the fifth to the upper border of the eighth thoracic vertebra. The laminae of the seventh vertebra were soft and appeared to be involved in the malignant process. The mass filled the entire epidural space and merged at either end with the epidural fat. The maximum thickness of the tumor was from 0.6 to 0.7 cm. A ribbon-like strip of the tissue was removed to unroof the dura. The wound was closed with silk.

Histologic Examination.—The tumor tissue was composed of anaplastic cells set in a delicate reticular network. The nuclei were large and vesicular. Many dense hyperchromatic nuclear masses, atypical mitotic figures and multinuclear cells were present. The tumor was considered to be a reticulum cell sarcoma (fig. 3 *B*).

Course.—The immediate postoperative course was uneventful. Two days after operation the patient could appreciate pinprick over the lower extremities in a relatively normal manner. Four days later he was able to void voluntarily. Sixteen days after operation he could stand with assistance and was discharged from the hospital on September 21, one month after the operation. There was gradual improvement, and by November 1933 he could walk unassisted. Roentgenotherapy was instituted, but an inadequate amount was given owing to the uncooperativeness of the patient. Two months after operation enlargement of the lymph nodes in the left axilla was found. The nodes rapidly increased in size, and on Feb. 25, 1934, one was removed surgically for histologic study. Microscopic examination showed tumor tissue identical in structure with that removed from the spinal epidural space. The patient became anemic and slowly lost weight and strength. Large rounded masses now appeared in the right lower part of the abdomen, and both the liver and the spleen became palpable. Jaundice and ascites were present shortly before death, in November 1934. It is of interest to note that motor power in the lower extremities and the ability to urinate were retained to the end.

This is an example of a widespread malignant disease in which the spinal epidural space was involved before the disease manifested itself by glandular enlargement. The secondary anemia and asthenia in a young man suggested that the obvious implication of the spinal cord was a local expression of widespread disease. The invasion of a vertebral arch, seen at operation although not disclosed by roentgenography, is a common observation with this type of tumor as well as with the various other neoplasms under discussion. The reticulum cell sarcomas are known to be more radioresistant than the types illustrated by cases 1 and 2; however, this patient's failure to cooperate prevented a fair trial of roentgenotherapy. The treatment given the tumor-bearing area, although small in amount, at least seemed to prevent a return of symptoms of involvement of the spinal cord.

CASE 4.—*Pain in the left lower extremity; later in both lower extremities and the back. Rapid progress of symptoms; inability to walk at the end of two months. Laminectomy. Lymphosarcoma. Improvement. Roentgenotherapy. One month following laminectomy pain in the neck and weakness of the upper extremities. Quadriparesis. Death six months after onset of initial symptoms.*

C. L., a man aged 27, was admitted to the hospital on March 30, 1935, complaining of sharp, shooting pains in the thighs and legs. He had been in good health until Dec. 27, 1934, when he first noticed an intermittent pain about the inner aspect of the left knee. Within a week from the onset the entire left lower extremity was so painful that he walked with a limp. Approximately two weeks later the patient began to have a dull ache in the lower part of the back and at this time experienced exacerbations of pain in the left leg when coughing or sneezing. One month after onset of pain in the left lower extremity, pain similar in character and distribution was noted in the right lower extremity. During the next ten days the legs became progressively weaker; the sharp, shooting pains became more severe, and the feet were numb. The patient was compelled to remain in bed most of the time until March 1935, when the lower extremities became so weak that he could not stand alone. There had not been any disturbance of the vesicular or anal sphincter.

Examination.—The patient was well nourished. He complained that the slightest movement of the lower extremities caused a burning, shooting pain in the thighs and legs. The head, cranial nerves, neck and upper extremities showed nothing abnormal. No enlargement of the cervical, axillary or inguinal lymph nodes was present. The abdominal reflexes were elicited in all quadrants and were equally active on the two sides. The cremasteric reflexes were not obtained. The liver and spleen were not palpable. The lower extremities showed marked loss of motor power in all muscle groups. The knee, hamstring and ankle jerks were not obtained. From the cutaneous area supplied by the twelfth thoracic nerves downward there was diminished perception of superficial touch and painful stimuli. Deep sensibilities were likewise impaired. Strong cutaneous stimulation, such as the deep thrust of a pin, caused a widespread burning pain. The external anal sphincter could be contracted voluntarily. There was moderate tenderness over the posterior spinous processes of the lower thoracic and upper lumbar vertebrae. There was no remarkable spasm of the lumbar muscles. The patient was unable to stand alone. Examination of the blood revealed 4,200,000 red and 7,800 white cells per cubic millimeter, and the hemoglobin was 85 per cent (Sahli).

No abnormal white cells were seen. Urinalysis gave results within normal limits. The Wassermann reactions of the blood and spinal fluid were negative. A spinal puncture performed in the fourth lumbar vertebral interspace disclosed xanthochromic fluid, and a complete block of the spinal subarachnoid space was demonstrable by jugular compression. Roentgenographic examination of the entire vertebral column and the thorax disclosed no abnormal findings.

Operation.—On April 4 laminectomy of the twelfth thoracic and first, second and third lumbar vertebrae was performed. A bluish gray, rather vascular and obviously infiltrating tumor was exposed. It filled the epidural space posteriorly, extending from the level of the middle of the twelfth thoracic to the middle of the third lumbar vertebra. At either end it fused with the epidural fat and extended laterally as far as could be visualized. The dura was unroofed by removing a ribbon of tumor the width of the laminectomy opening. The dura was opened, but this structure was not grossly invaded, nor was there a demonstrable intradural lesion. The wound was closed with silk.

Histologic Examination.—The tumor was composed of diffusely distributed cells with pyknotic nuclei and scanty cytoplasm. The nuclei were somewhat larger and the cytoplasm more abundant than in normal lymphocytes. Mitotic figures were numerous (fig. 3 *C*). The neoplasm was considered to be a lymphosarcoma.

Course.—The patient made no complaints of pain in the lower extremities throughout the rest of his stay in the hospital. He was allowed out of bed on the tenth day after operation and was discharged from the hospital on April 17, with instructions to report for radiation therapy. Four days after discharge he became aware of pain in the neck, radiating over the lateral aspect of the shoulders and arms. Within three days he lost the use of his hands and could no longer walk. He was readmitted to the hospital on April 27. Examination at this time showed hypalgesia and hypesthesia from the level of the sixth cervical dermatome down, presence of biceps reflexes, loss of triceps and radial reflexes, marked weakness of extension and flexion of the fingers of both hands, absence of abdominal and cremasteric reflexes and incontinence of urine without demonstrable distention of the urinary bladder. The knee jerks were obtained, but the hamstring and ankle jerks were not demonstrable. Roentgenographic examination of the thorax and the cervical portion of the spine showed no evidence of new growth. Roentgenotherapy was given to the entire vertebral column from May 1 to 24. Four fields were used, and a total of 2,660 roentgen units was administered during the period of treatment. Complete paralysis of all four extremities ensued, with loss of all modalities of sensation from the level of the sixth cervical spinal segment down. The patient was taken home on May 25 and died one month later, approximately six months after the onset of the first symptom.

In this instance, as will be noted in case 6, there were signs that indicated invasion of the epidural space at two levels. Although the nature of the lesion which produced the physiologic interruption of the spinal cord in the cervical region was not proved histologically, the clinical evidence strongly suggests that it was the same as that observed in the lumbar area. Roentgenotherapy was given to the entire spinal axis, since cervical laminectomy did not seem advisable. We have noted in similar instances of compression of the spinal cord by radiosensitive tumors that irradiation does not result in restoration of function of the spinal cord.

CASE 5.—*History of trauma. Pain in the back radiating into the anterior part of the left thigh; absence of lumbar lordosis; paresis of the lower extremities. Laminectomy. Hodgkin's disease. Roentgenotherapy. Clinical recovery.*

D. K., a man aged 48, was admitted to the hospital on June 18, 1937, complaining of pain in the lower part of the back radiating into the left thigh. Three months before entrance to the hospital he slipped on a stairway while carrying an armful of bundles and fell forward, but did not lose his footing. Immediately there was pain along the inner aspects of the thighs, and this continued intermittently, increasing in severity for the next two months. Three weeks prior to admission pain was first noted across the upper lumbar region of the back, with an occasional sharp shooting pain into the anterior aspect of the left thigh. Any torsion or bending movement of the spine aggravated the pain in the back, which was described by the patient as a "catch." One week following the onset of pain in the back it became necessary to use a cane when walking. The pain was so severe in the recumbent position that sedation was required. There had been no subjective sensory disturbances except a feeling of numbness along the frontal aspect of the left thigh. No disturbance of vesicular or rectal control had been noted.

Examination.—The patient was well built, but somewhat undernourished, and moved in bed with caution. The superficial lymph nodes were not abnormally large. Examination of the head, neck, upper extremities and trunk showed nothing noteworthy. The lumbar lordosis was obliterated, and the posterior spinous processes of the lumbar vertebrae were prominent. The lumbar portion of the vertebral column was held in a fixed position, and any attempt to flex or extend the spine caused pain. All the abdominal reflexes were present; the cremasteric reflex was obtained on the right but was absent on the left. The lower extremities were mildly paretic. Any voluntary movement of these extremities was performed in a guarded manner. The knee, hamstring and ankle jerks were brisk, slightly more so on the right side. A Babinski sign was not demonstrable. All modalities of sensation were within normal limits, except for slight diminution in the appreciation of vibratory stimuli bilaterally. Examination of the blood and urinalysis gave normal results. The Wassermann reactions of the blood and spinal fluid were negative. Roentgenographic examination of the lungs and the vertebral column showed no abnormalities. Spinal puncture at the third lumbar vertebral interspace disclosed faintly xanthocromic cerebrospinal fluid, and a complete block of the spinal subarachnoid space was demonstrable by jugular compression. Roentgenographic examination of the vertebral column subsequent to the introduction of 0.5 cc. of iodized poppyseed oil into the cisterna magna showed the spinal subarachnoid space to be partially obstructed at the level of the eleventh thoracic vertebra (fig. 4).

Operation.—On June 30 laminectomy of the eleventh and twelfth thoracic and the first lumbar vertebrae was performed. A bluish, moderately vascular tumor was exposed, filling the epidural space and extending lengthwise over about two and one-half vertebral segments. At either end the tumor tissue faded into firm spinal epidural fat. Laterally the tumor extended as far as could be visualized. A strip of tissue corresponding to the length of the tumor and the width of the laminectomy opening was removed. The dura was opened, leaving the arachnoid intact. The wound was closed with silk.

Histologic Examination.—Portions of the specimen disclosed almost complete replacement of the epidural adipose tissue by a new growth of granulomatous character (fig. 3*D*). Cellular areas showed hyperplasia of the reticulum cells

and dense collections of lymphocytes, eosinophils and other leukocytes. There were also scattered areas of fibrosis. The tissue was regarded as that of Hodgkin's disease.

Course.—The postoperative course was uneventful, and the patient was allowed out of bed on the eleventh day after operation. Roentgenotherapy was instituted on the twelfth postoperative day, and during the ensuing month 3,900 roentgen units was given. At present, seven months after operation, the general condition is excellent, and there are no findings to indicate further extension of the disease.

The clinical history of this patient strongly suggested that protrusion of a nucleus pulposus had produced the symptoms and signs described.

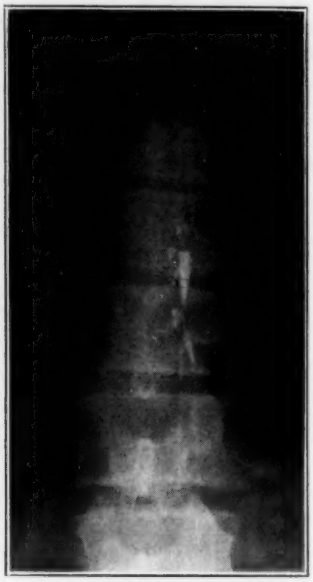

Fig. 4.—Roentgenogram showing the contrast medium (iodized poppyseed oil) retarded in its descent at the midpart of the eleventh thoracic vertebra (case 5).

The myelographic findings, however, indicated that the lesion was probably an epidural neoplasm, as was subsequently proved. The patient is to receive further roentgenotherapy.

CASE 6.—*Pain in the back; later bilateral midthoracic radicular pain; paraplegia. Laminectomy. Plasma cell myeloma. Freedom from symptoms for twelve months. Paresthesia and weakness in the upper extremities. Widespread involvement of the bones. Death.*

P. Y., a man aged 50, was admitted to the hospital on Oct. 5, 1933, complaining of pain in the back radiating around the chest and paralysis of the lower extremities. He had been in good health until the latter part of August (six weeks before entrance), when, while at work, he noticed a dull ache "between the shoulder blades." The jolting of the bus in which he rode to and from work increased the pain in the back to such an extent that he was compelled to

give up his position. After three weeks there was radiating pain around the mid-thoracic area. It was thought that the thoracic pain was pleurisy, for which he was treated. One month after onset of the pain in the back, the legs became weak and the gait unsteady. The patient walked with the aid of a cane for another week, at the end of which time it was necessary for him to remain in bed. The radicular pain ceased when the paralysis of the lower extremities became complete. There had been no difficulty in urination or defecation.

Examination.—The patient was well nourished with complete paralysis of the lower extremities. Examination of the head, neck and upper extremities presented no abnormal findings. Caudad to the level of the eighth thoracic dermatome there were loss of all volitional movements and complete inability to appreciate painful and thermal stimuli. Appreciation of touch over these areas was about 25 per cent of normal, and vibratory stimuli applied to the bony prominences were just perceptible. Hyperreflexia, a Babinski sign and patellar and ankle clonus were demonstrable in the lower extremities. The urinary bladder was not distended, and the patient was able to urinate. Examination of the blood showed 4,300,000 red and 11,000 white cells per cubic millimeter, and hemoglobin concentration was 85 per cent (Sahli). Urinalysis showed a trace of albumin. The urine was not tested for Bence-Jones protein. Roentgenographic examination of the vertebral column disclosed osteoarthritic changes. The Wassermann reactions of the blood and spinal fluid were negative. A spinal puncture in the third lumbar interspace showed xanthochromic cerebrospinal fluid, and a block of the spinal subarachnoid space was demonstrable by jugular compression. Following the spinal puncture there was incontinence of urine and feces, with complete anesthesia and analgesia below the level of the eighth thoracic dermatome.

Operation.—Laminectomy, performed on October 11, revealed an oval, pinkish tumor, measuring 3 by 3 by 2 cm., situated in a socket-like cavity in the base of the posterior spinous process of the seventh thoracic vertebra. The mass had compressed the dura and replaced the spinal epidural fat at this level. The neoplasm had invaded the lateral confines of the epidural space; therefore complete removal was not possible.

Histologic Examination.—Microscopically, the tumor tissue was composed of cells resembling plasmacytes, rather diffusely distributed in a scanty stroma. Occasional trabeculae of edematous vascular connective tissue were present. Many of the tumor cells showed the typical cartwheel nucleus, eccentrically placed and often bulging slightly beyond the generally ovoid cell outline. The cytoplasm of these cells was also that of the usual plasma cell seen in inflammatory processes. In many of the cells, however, there was more or less variation from this appearance. Mitotic figures were fairly numerous, and occasional large multinuclear forms were observed. The histologic diagnosis was plasma cell myeloma.

Course.—The postoperative course was uneventful, and the patient was allowed out of bed on the fourteenth day. Normal control of the urine and feces was established within three weeks after operation. The patient was discharged from the hospital on November 19. The motor power in the lower extremities slowly returned, and he was able to walk with the aid of a cane. The abnormal sensory findings likewise regressed, and when the patient was examined three months after operation there were no demonstrable residual symptoms. The record failed to mention whether roentgenography was suggested. The patient did not return for further examination, and the next observation was made on Nov. 26, 1934, after his admission to a city hospital. At this time there were pain and numbness of the forearms and hands and a clumsy feeling in the lower extremities. Exami-

nation disclosed loss of skilled movements of the hands. No loss of cutaneous sensation was recorded. The deep reflexes of both upper and lower extremities were very active, and a Babinski sign was obtained bilaterally. Roentgenographic examination disclosed a large mediastinal mass and osteolytic involvement of the clavicles, right scapula, lower ribs on the right side, left ilium and tenth and eleventh thoracic vertebrae. No evidences of bony changes in the cervical vertebrae were seen. Roentgenotherapy was suggested, but the patient signed his release from the hospital. He died at home during the latter part of February 1935.

The microscopic structure was that seen in most instances of multiple myeloma; that is, tumor tissue composed of cells resembling plasma cells. The case is included in this group of lymphomatoid diseases

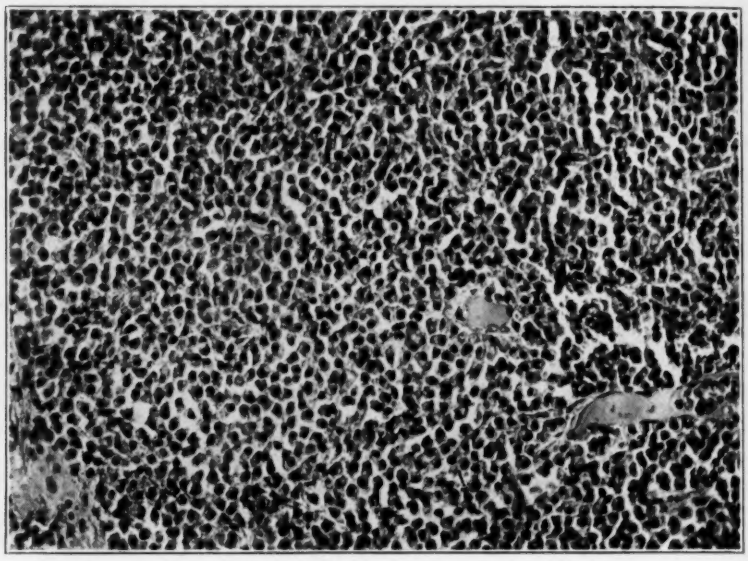

Fig. 5.—Myeloma invading the spinal epidural space (case 6). The regular distribution of cells and their resemblance to plasma cells are characteristic microscopic features.

because of the possibility that the cell or cells of origin may be one or another of the myeloid elements and that the process may therefore be related to the myeloid leukemias. If, on the other hand, the various types of multiple myeloma are considered to originate from the plasma cell. an adventitial cell of the vascular walls, the inclusion of the case in this series does not seem justified.

Of the remaining 6 patients, 1 died the day after operation, and another who had pyelonephritis died on the sixteenth postoperative day. The clinical course in 3 other cases was similar to that in case 4, the periods of survival being two, three and four months, respectively. A

sixth patient is now convalescing from laminectomy. Histologically, the tumors in all 6 cases were lymphosarcomas of small or large cell type.

COMMENT

An adequate anatomic account of the spinal epidural space and a histologic description of the fat, blood vessels and lymphatic channels which anatomists have briefly stated to be present in this space are not available. Luce [4] mentioned that the spinal epidural space contains adipose tissue and an arteriovenous plexus "with accompanying lymphatics." Iwanow and Romodanowsky [5] reported on experimental results concerning the relation of the cerebral and spinal submeningeal spaces to the lymphatic system. They observed that various substances in hypertonic solution when injected into the spinal subdural space passed into the lymph space and lymph capillaries of the dura mater and also reached the fatty layer of the epidural space. The injected substance passed from here into the extravertebral lymph nodes.

No information is available regarding the presence or absence of lymphoid tissue in the normal spinal epidural structures. Personal examination of the spinal epidural tissues taken at autopsy from persons who had met accidental death have failed to show any aggregation of lymphatic cells. This study has not been sufficiently extensive to warrant a conclusive statement on this point, but indicates that lymphocytic elements are at least not commonly seen in this location.

Dissections of autopsy material have shown that the spinal epidural space extends from the upper border of the dorsal arch of the atlas throughout the length of the dural sac, to merge with the fat-filled space in the sacral vertebral canal. (Since the dural envelop terminates at the level of the second sacral vertebral segment, the space caudad to this cannot in a strict sense be termed epidural.) In cross section the epidural space is crescentic and is bounded anteriorly and mesially by the dura mater and dorsolaterally and dorsally by the ligamentum flavum and the segmentally interposed periosteal coverings of the vertebral arches. Normally, the space does not extend over the anterior face of the dura, since the dura mater throughout its length is loosely attached to the posterior longitudinal spinal ligament. The most anterior limit of the space is at the lateral border of the posterior longitudinal spinal ligament, except at the sites of the dural prolongations about the spinal nerves. Here the limits of the space are ill defined. A potential continuation of the space exists between the dural coverings of the spinal nerves and the

4. Luce, H.: Zur Klinik des extraduralen spinalen Räumes, Deutsche Ztschr. f. Nervenh. **78**:347, 1923.

5. Iwanow, G., and Romodanowsky, K.: Ueber den anatomischen Zusammenhang der cerebralen und spinalen submeningeal Räume mit dem Lymphosystem, Ztschr. f. d. ges. exper. Med. **58**:596, 1927.

linings of the intervertebral foramens. There is a departure from this arrangement in the sacral portion of the vertebral canal, which has no significant bearing on the subject under discussion. The greatest depth of the spinal epidural space is in the midline, as has been indicated; measured by its fat content, the depth of the space gradually increases from the cervical limits to the lower lumbar region, where the fat layer measures from 0.4 to 0.6 cm. in thickness.

Malignant tumors may arise from the spinal epidural tissues (space) or may implicate these tissues by various routes, namely, (1) by direct invasion from an area of contiguous involvement of bone, (2) by extension through the intervertebral foramens or (3) by hematogenous, and possibly lymphogenous, implantation from distant sources. Extension from metastatic carcinomatous lesions of the vertebral column is probably the most common mode of involvement. In other generalized malignant processes, such as the various so-called lymphomatoid diseases, the route of invasion of the epidural tissue offers more difficulty of explanation. Direct extension from regional lymph nodes by way of the intervertebral foramens seems the most logical concept, but primary origin in the epidural tissue must be considered as a possibility. Although no lymphoid elements have as yet been demonstrated within the space, their ubiquitous distribution suggests that small foci may at times be present as normal constituents.

Except for the single example of myeloma, the tumors visualized at operation were of strikingly similar appearance. They filled the spinal epidural space, were poorly delineated at each end and partially encircled the dural envelope (fig. 6). Their color varied with the vascularity; in general, the more vascular the greater the degree of malignancy. Examination of the excised tissues failed to show any gross characteristics of noteworthy distinction except that each specimen consisted of an irregular cellular growth. Histologically, precise diagnosis in many instances was also impossible, and the group designation of lymphomatoid diseases was employed. In several cases, however, a more exact classification seemed warranted on initial examination.

The giant follicular lymphadenoma (case 1), an entity described by Brill, Baehr and Rosenthal[6] was readily identified on the basis of the microscopic structure of the tissue. Recognition of this type of tumor, which seems to occupy a position between the benign lymphadenomas and the highly malignant lymphosarcomas, is of considerable prognostic value both because of its relatively slow clinical course and of its sensitivity to radiation therapy. We have been unable to find any other

6. Brill, N. E.; Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of the Lymph Nodes and Spleen, J. A. M. A. **84**:668 (Feb. 28) 1925.

recorded instance of the occurrence of a neoplasm of this variety within the vertebral canal. Case 5 was considered an example of Hodgkin's disease because of the rather marked granulomatous character of the excised tissue. There have been as yet no clinical developments either to refute or to confirm the opinion regarding this tissue. It is possible that in the hands of others this specimen might be classified differently. In case 3 the lesion was obviously neoplastic, the tumor cells being of large lymphocytic type but very anaplastic. Case 4 was interpreted as an instance of reticulum cell sarcoma, an entity recently distinguished from the large cell (lymphoblastic) lymphosarcomas and grouped with the monocytic leukemias under the designation of the reticuloses.[1] The tissue

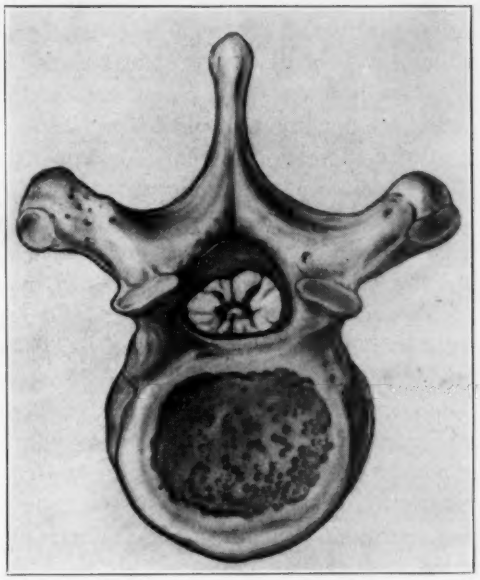

Fig. 6.—A cross sectional representation of our concept regarding position, extent of implication and manner of compression of the spinal cord in instances of spinal epidural lymphoblastic tumors.

in the case of multiple myeloma also showed distinctive microscopic characteristics, as previously described. In several of the remaining cases the original histologic diagnosis was "some type of lymphoblastic tumor," and a review of the tissue sections indicated that no more specific designation of the tumor type was justified at the time. The remaining 6 cases in this series, not included in the illustrative group, were examples of lymphosarcoma of both small and large cell types. It may therefore be stated that microscopic examination of these specimens furnished, in the light of available clinical data, information of definite prognostic value. The necessity in some instances of resorting to the tentative

diagnosis of some type of lymphomatoid disease did not in the least delay the institution of postoperative therapeutic measures.

As the initial clinical manifestations of these lymphomatoid diseases may indicate compression of the spinal cord or cauda equina, there should be no question regarding the advisability of surgical exploration. When the implication of the spinal cord is a late occurrence during the course of a known generalized malignant disease, the indications for or against surgical treatment should be decided on the merits of the individual case. A life expectancy of from six to eight months and a reasonable outlook for the recovery of paretic or paralytic extremities warrant palliative partial surgical removal of a spinal epidural tumor although of suspected malignant character. This attitude toward all tumors encountered within the vertebral canal will tend to change guarded mortality statistics and no doubt will modify the present accepted belief that most tumors of the spinal cord offer a favorable prognosis. It is intended not to suggest that a useless operation should be performed on any patient who presents signs of compression of the spinal cord, regardless of the etiologic factor, but to point out that malignant tumors arising within or invading the vertebral canal require far greater therapeutic consideration than do the relatively easily extirpated benign tumors.

In the treatment of the lymphomatoid diseases of the spinal epidural space, the use of all available methods, surgical and roentgen therapy being the two outstanding measures, will often be followed by disappointing results. However, an unexpectedly long period of survival (cases 1 and 2) may ensue after proper therapy has been given. When an ill defined, malignant-appearing mass is uncovered at operation, the tumor should be widely exposed and the dura unroofed by removing a strip of the neoplastic tissue the full length of the tumor and the width of the laminectomy opening. The dura should be incised over a distance corresponding to the length of the tumor and should be left open. Excision of a portion of the tumor releases the compression of the intradural structures and provides space for the possible expansion of the remaining malignant tissue following the initial radiation treatment. Partial removal of the tumor with the resultant prompt mechanical release of the intradural contents followed by adequate irradiation gives an earlier and more satisfactory recovery than roentgenotherapy alone. Many patients who have harbored one of the types of lymphomatoid diseases have not been given the benefit of adequate roentgen treatment. This was true in some cases of this series. While a cure cannot be promised any patient with this disease, an ambulatory existence for the remaining months of life can be restored to some and an indefinite period of survival given to others by the judicious employment of the available therapeutic measures.

SUMMARY AND CONCLUSIONS

A series of 12 cases representing some of the various types of lymphomatoid disease of the spinal epidural space has been reviewed. The initial symptoms and signs in each instance indicated implication of the spinal cord or cauda equina. All the patients had been operated on at a time when there was no demonstrable evidence of involvement of other structures. There was seen in each case a malignant growth in the spinal epidural space.

The anatomic confines and the structures within the spinal epidural space have been briefly described. The various modes of invasion of malignant neoplasms have been considered, and the possibility of lymphoblastic tumors originating primarily in the epidural tissues has been suggested.

Histologically, these tumors were examples of lymphosarcoma, of small and large cell types, giant follicular lymphadenoma, reticulum cell sarcoma, Hodgkin's disease and multiple myeloma. At the time of operation, microscopic examination of the tissues permitted an exact diagnosis of prognostic value in some instances, while in others the group designation of lymphoblastoma was employed pending further clinical developments.

Surgical unroofing of the involved portion of the vertebral canal by laminectomy and partial excision of the epidural tumor, followed by intensive roentgenotherapy, resulted in the survival of 2 patients for periods of four and one-half and two and one-half years, respectively. A third patient, operated on seven months ago, is now receiving roentgenotherapy, and a fourth, recently operated on, is to receive similar treatment. In the remaining 8 cases radiation therapy either was given in doses far less than we think should have been employed or, for various reasons, was not used at all. In several of these 8 instances a period of ambulatory existence was restored.

SPECIAL ARTICLES

THOMAS WILLIS ON NARCOLEPSY

WILLIAM G. LENNOX, M.D.
BOSTON

The assignment of priority in the description of any disease is a perilous matter because it is dependent on the thoroughness with which the writings of old authors are perused. Credit is commonly given to Westphal (1877) for first describing narcolepsy and to Gélineau (1880) for naming it. However, Gélineau himself cited a case reported by Caffe in 1862. Wilson [1] stated that Graves reported a case in 1851, and Cave,[2] that Richard Bright performed an autopsy (the only one ever recorded) on a patient with narcolepsy in 1836.

> This woman, aged 67, had been a patient of Bright's for ten years. For from thirty to forty years she had had attacks of sleep characteristic of narcolepsy. In addition, for an unstated period she had had "shaking fits" in which her hands would be agitated, her head would fall, as if the muscles of the neck had lost all power, and her features would become distorted. By dint of being dragged about the room she would be "gradually brought to herself." Bright's autopsy disclosed a tumor of the dura, the size of a filbert, which pressed into the right hemisphere, ossification of the internal carotid arteries, a hemorrhage into the optic thalamus and corpus striatum on the left and blood in the ventricles. Bright ascribed the attacks of sleep to calcification of the carotid arteries and the "shaking fits" to the dural tumor. "We know that irritation upon the surface of the brain from disease or accident will apparently become the cause of epilepsy."

Cave expressed the belief that the "shaking fits" were the cataplectic attacks of narcolepsy and that Bright erred in ascribing them to the intracranial tumor. However, an emotional precipitant of these attacks was lacking; a great deal of muscular spasm and intracranial pathologic change was present, and Richard Bright was an astute observer. Therefore it seems that his diagnosis should not lightly be set aside. Doubt may be entertained, however, whether any of the observed pathologic lesions caused the sleeping attacks which began thirty or forty years before.

As a positive contribution to this subject, I wish to point out that Willis described narcolepsy (without, however, mentioning cataplexy)

From the Department of Neurology, Harvard University Medical School, and the Neurological Unit of the Boston City Hospital.

1. Wilson, S. A. K.: The Narcolepsies, Brain **51**:63-109 (March) 1928.
2. Cave, H. A.: Narcolepsy, Arch. Neurol. & Psychiat. **26**:50-101 (July) 1931.

more than two hundred years before Westphal. Thomas Willis (1621-1675) was made professor of philosophy at Oxford in 1660 and from 1666 was a popular London physician. He made careful pathologic studies of the central nervous system, which find commemoration in the "circle of Willis." He wrote, of course, in Latin. In 1672 he published "De anima brutorum."[3] The quotations which follow are from the English translation of his complete works by Samuel Pordage, printed in London in 1684.[4] The chapter of the "De anima" from which I quote is headed: "Of Some other Sleepy distempers. viz. a continual Somnolency, the Coma, or heavy Sleeping; and the Caros, or a deprivation of the Senses."

First, Willis described the chief symptom and pleaded recognition for it as a disease entity.

> Most Authors call this [continual sleepiness] not a Disease, but an evil habit, or a sleepy disposition, for the distemper'd, as to other things, are well enough; they eat and drink well, go abroad, take care well enough of their domestick affairs, yet whilst talking, or walking, or eating, yea their mouths being full of meat, they shall nod, and unless rouzed up by others, fall fast asleep: and thus they sleep continually almost, not only some days or months, but (as it is said of Epemenides) many years; wherefore we ought to believe this a Disease, and worthy of Cure, which defrauds one of more than half his life.

Willis then stressed the normalness of patients between attacks and discussed the localization of the disturbance in the brain, arguing that only the cortex is involved.

> It differs not only from the Lethargy, but the Coma also; for in the Distempers which we described, though continual sleep presses on them, yet 'tis easily broken off; then besides, being fully awakened they remember many things, and converse with their Friends, though immediately prone again to sleep: whence it appears, that the cause of this Disease sticks only in the outer border of the Brain, nor does it enter deep into its compass, as other sleepy distempers do.

Then follow the pathophysiologic changes in the condition: first, cerebral edema and then an increase in intracranial pressure, followed by stasis in the flow of cerebral blood. Finally, because of this vascular stasis, the cerebrospinal fluid which nourishes the subcortical areas carries sleep-producing elements to them.

> But indeed it may be suspected, that while the Blood every where washing the border of the Brain, with thick rivulets, and instils every where into it a subtil

3. Willis, T.: De anima brutorum quae Hominis vitalis ac sensitiva est, exercitationes duae: Prior physiologica ejusdem naturam, partes, potentias et affectiones tradit; altera pathologica morbos qui ipsam, et sedem ejus primariam, nempe cerebrum et nervosum genus afficiunt, explicat, eorumque therapeias instituit, London, R. Davis, 1672.

4. Willis, T.: Practice of Physick, London, T. Dring, C. Harper and J. Leigh, 1684.

water, for the matter of Spirits, oftentimes a great plenty of water flowing thither with it, and entering together the Cortex, and remaining there, mightily fills it, and (like an Anasarca in the Body) swells it up: But this Cortical or shelly part being swelled up after this manner, and as it were dropical, so presses the Medullary infoldings, every where lying under it, that the expansion of the Spirits being hindered, by reason of the Pores of the exterior part of the Brain being something bound up, sleepiness is induced; to which it happens, that the Blood, that by reason of the Cortex of the Brain being intumefied with water, as it were between the Skin, Circulates less expeditiously, thorow all the neighbouring parts, and so is apt to fill the Vessels and bosoms, and to stagnate in them; by which means it comes to pass, that the exterior border is yet more compressed, and so the spaces requisite for the emanation of the Spirits, are also more streightened. Indeed this appears to be part of the cause, from hence, because this kind of sleepiness, by reason of the Blood not freely circulating in the Head, and therefore apt to stagnate, is wont to make red the Face, with a certain blueness and blackness: Further, whilst the subtil Liquor, which is for the matter of Spirits, passing thorow this pond or deluge heaped together in the Cortex of the Brain, goes forward into the Marrow lying under, it is probable, that with it do creep thorow some extraneous, and as it were very small Narcotick particles, which growing to the Spirits immediately render them torpid or stupid, and prone to sloth of their own accord.

The prognosis for life is good, and cure often takes place, though various symptoms of neurosis remain.

This Distemper, as I have observed in many, is not very dangerous, for as it often happens, it is wholely Cured, or at least remaining for many years, without the Carus or Apoplexy (which is wont to be feared) it doth not become mortal or terrible. The Cure of this Disease often happens, the seat of it being changed, to wit, when clearing the Brain, the Morbific Matter is transferred to the Cerebel, which coming thither, produces tremblings of the Heart, the Asthma, loss of Spirits, and other troublesome Symptoms, commonly taken for Hypochondriacal.

With regard to treatment, which neither Westphal nor Gélineau considered, Willis advised reduction of cerebral edema by phlebotomy and purges.

Further, it is expedient that two large Issues be made between the Shoulders, and also frequent Blistering Plasters be applied about the Neck. The hair being cut off, let a quilted thing of Cephalicks and Spices be worn under the Cap. Let them also hold their noise [i. e., nose] often over a Vessel fill'd with Salt of Urine, or the Spirit of Sal Armoniack; let care be taken that they keep to an exact order of diet, and that those attending the sick, do not only rouse them from sleep, but daily at some set hours keep them waking.

As for medication, in addition to decoctions of various herbs, Willis prescribed a drink which he did not give for other types of sleep disorders, viz., coffee.

At eight of the Clock in the Morning, and at five in the Afternoon, let them drink a draught of Coffee, or the Liquor prepared of that Berry, first boiling in it, the leaves of Sage or Rosemary, till it has got a greenish Tincture.

Then followed the report of a case.

A certain Gentleman of a Sanguine Complexion, and when he was young, of a sharp and cunning wit, but afterwards growing aged, being given to idleness and drunkenness, became dull and stupid, and also Dropsical, with a great paunch, and his thighs and legs swelled. Yet from these Diseases (which he frequently fell into) when he abstained at any time from drinking, and took Physick, he oftentimes quickly grew well. But at length, though he was freed from the Dropsie, he was oppressed with so heavy a sleepiness, and that almost perpetually, that in what place soever he was, or what ever he was doing he would sleep; then being awakened by his Servants or Friends, his mind appeared well enough, and for a few minutes he would discourse of any thing well enough, then immediately fall again to sleep.

In accordance with Willis' advice:

When he would indulge himself by Drinking, instead of Wine or Beer, he drunk Coffee; but for his ordinary drink, he had sometimes Ale, with the leaves of Scurvigrass, Sage, and Spices infused in it; and sometimes with Woods, Spices, and Cephalick Herbs boiled with it: He lived thus for many years after, almost always intemperate, and full of gross humors, yet free from the Lethargy; at length a Cachexy or evil state of Body invading him, and wasting with a Cough and Asthma, by degrees, he dyed.

Probably the autopsy material of Willis, like that of Bright, provided information about the cause of death rather than the cause of the antecedent pathologic sleep. Of more clinical interest is Willis' use of coffee. Not until Janota,[5] in 1930, and Doyle and Daniels,[6] in 1932, independently introduced ephedrine sulfate was a preparation superior to caffeine available.

A careful search of ancient writings would probably bring other descriptions of narcolepsy to light. Indeed, Willis himself mentioned the case of Epimenides, the Cretan poet who lived in the seventh century, B. C., and slept in a cave for fifty-seven years!

---

5. Janota, O., cited by Daniels, L. E.: Narcolepsy, Medicine **13**:1-122 (Feb.) 1934.

6. Doyle, J. B., and Daniels, L. E., cited by Daniels, L. E.: Narcolepsy, Medicine **13**:1-122 (Feb.) 1934.

Case Reports

SUDDEN "BRAIN DEATH" IN SCHIZOPHRENIA WITH EXTENSIVE LESIONS IN THE CEREBRAL CORTEX

N. Malamud, M.D., and David A. Boyd Jr., M.D., Ann Arbor, Mich.

Sudden "brain death" occurring in various psychoses is reported in the literature under the designations of "delirium acutum," "délire aigu," "tödliche Katatonie" and others. The symptoms and clinical course of this condition are apparently uniform, but there is no agreement as to its classification. Ladame [1] and Redalié [2] stated that the disorder is based on clinicopathologic findings which they classed as specific, while Scheidegger [3] and Jahn and Greving [4] expressed the belief that it is a syndrome and complication of various psychoses, usually schizophrenia. Stauder [5] expressed the opinion that it is a definite disease unit because it usually occurs in hereditarily tainted persons with constitutional vasomotor instability who are otherwise physically and mentally normal.

CLINICAL FEATURES

The onset is abrupt; the duration is brief, usually from several days to a few weeks, and the outcome is always fatal. The symptoms are both mental and physical, the latter frequently overshadowing the former.

The mental picture in the majority of cases is characterized by violent motor excitement, an anxious apprehensive affect and clouding of consciousness. The most outstanding symptom is the excitement, which is characterized by continual aimless activity and unrest, with sudden impulsive outbursts of assaultiveness or suicidal attempts and in some cases by incoherent choreiform movements or states of rigidity. The anxiety, which may precede the excitement, is apparently unrelated to any depressive content of thought and in its intensity suggests an "endogenous" panic reaction. The disturbances in consciousness con-

From the Neuropsychiatric Institute, University of Michigan, R. W. Waggoner, M.D., Director.

1. Ladame, C. H.: Psychose aiguë idiopathique ou foudroyante, Schweiz. Arch. f. Neurol. u. Psychiat. **5**:3, 1919.

2. Redalié, L.: Contribution à l'étude de l'anatomie pathologique du délire aigu idiopathique, Schweiz. Arch. f. Neurol. u. Psychiat. **7**:35, 1920.

3. Scheidegger, W.: Katatone Todesfälle in der psychiatrischen Klinik von Zürich von 1900 bis 1928, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:587, 1929.

4. Jahn, D., and Greving, H.: Untersuchung über die körperlichen Störungen bei katatonen Stuporen und der tödlichen Katatonie, Arch. f. Psychiat. **105**:105, 1936.

5. Stauder, K. H.: Die tödliche Katatonie, Arch. f. Psychiat. **102**:614, 1934.

sist of confusion and stupor, ultimately terminating in deep coma. In some cases there are rapidly developing collapse and coma without a preceding period of excitement. In other cases repeated convulsive seizures may dominate the picture. Most authors have stated that these phenomena are an expression of an organic disorder of the brain and minimized the psychogenic element, especially since the content of thought is negligible.

The physical symptoms consist of striking metabolic, nutritional and vasomotor changes, which appear to be related to disturbances in central regulatory mechanisms. There are rapidly developing severe cachexia and dehydration, frequently accompanied with excessive perspiration and salivation. There is marked hyperpyrexia (104 to 105 F.) of the central type, the body temperature being elevated and the cutaneous temperature lowered. Respiration is often shallow and irregular; the cardiac action is at first rapid and strong, later becoming feeble and arrhythmic. Some authors (Jahn and Greving) have reported a fall in blood pressure, while others (Stauder) have observed hypertension (180 to 210 mm.). Neurologic signs as a rule are not prominent. The pupils are usually dilated and react sluggishly; tendon reflexes, at first exaggerated, gradually disappear.

Vasomotor phenomena and hematologic changes have been greatly emphasized in recent publications. Stauder stressed the constitutional vasomotor lability (hemorrhagic diathesis, menstrual disorders) which during the acute episode is manifested by the early appearance of acrocyanosis, spontaneous ecchymoses and hematomas in the skin and mucous membranes. Jahn and Greving emphasized the frequency of such signs of peripheral circulatory collapse and, in addition, reported the regular occurrence of associated changes in the blood and bone marrow. The blood shows a striking relative polycythemia, with an increase in the number of erythrocytes, and higher hematocrit readings and values for hemoglobin in the presence of a normal volume of blood. There is marked reticulocytosis, suggesting erythropoiesis, which in many cases is confirmed by transformation of the yellow into red bone marrow.

PATHOANATOMIC FEATURES

According to the majority of investigators, a marked discrepancy exists between the severity of the clinical manifestations and the mildness or even absence of pathoanatomic findings. Various explanations of the cause of death, such as exhaustion, inanition and terminal infections, are admittedly inadequate. Although the pathogenetic significance of central disturbances is commonly stressed, the results of anatomic studies of the central nervous system are either inconstant or are not generally accepted.

The most important findings reported in the literature can be summarized under the following headings:

Brain Swelling (Hirnschwellung).—This has been observed in cases of fatal catatonia as well as in cases of various acute disorders. According to Reichardt,[6] this condition is characterized by a sudden increase in the volume of the brain, not due to the presence of increased free fluid (edema, etc.) or to an intracranial expanding lesion, which leads

6. Reichardt, M.: Hirnschwellung, Allg. Ztschr. f. Psychiat. **75**:34, 1919.

to death through cerebral compression. Its pathogenesis and histologic substratum have remained unknown, but it is generally accepted that brain swelling is intravitally produced and bears a significant relationship to the fatal issue. Nevertheless, its occurrence in the disorder here discussed is comparatively rare (in 6 of Scheidegger's 39 cases; in none of Stauder's 27 cases). Goldstein [7] has expressed the opinion that pial edema is of greater significance than *Hirnschwellung,* similarly ascribing to it fatal effects through cerebral compression.

Diffuse Parenchymatous Changes.—Other observers have reported histologic changes in the cortex and basal ganglia and maintained that they are of sufficient intensity to constitute an anatomic substratum of the acute disorder. Ladame described severe degeneration and lipoidosis of neurons and perivascular infiltration by inflammatory cells, which he interpreted as true encephalitis. On the basis of similar findings, Redalié and Claude and Cuel [8] expressed preference for the theory that the condition is a toxic encephalopathy. Other authors (Josephy,[9] Goldstein) observed only generalized acute swelling of the neurons but implied a similar toxic process.

Josephy stated that acute fatal catatonia is merely an exacerbation of the general schizophrenic process, which, he maintained, has a definite anatomic substratum. According to him, the pathologic basis of chronic schizophrenia consists of focal acellular areas, especially in the third layer of the cortex, diffuse degeneration, lipoidosis and sclerosis of the neurons and proliferation of glia in the border zones of the gray and white matter. Josephy illustrated the relationship between the chronic and acute processes in a case of chronic schizophrenic deterioration in which there was a terminal fatal condition characterized by epileptiform seizures (case Eussner). Histologically he reported, in addition to acute swelling of the neurons and chronic acellular areas, focal accumulations of fat-laden atypical (Alzheimer) glia in the third layer of the frontal cortex and in the border zones of the gray and white substance. He regarded the latter changes as acute manifestations of the same process and of "local vulnerability," which characterized the pathologic picture of chronic schizophrenia.

Circulatory Disturbances.—In a variety of psychoses terminating in acute fatal episodes of excitement, Braunmühl [10] reported ischemic and necrotic lesions in the cortex or hemorrhages in the medulla oblongata, which he attributed to circulatory disturbances caused by spasm and stasis in the terminal branches of the blood vessels. These disturbances, according to Braunmühl, are not primary but are produced by the

7. Goldstein, K.: Zur pathologischen Anatomie der Dementia praecox im besonderen der plötzlichen Todesfälle bei derselben, Monatschr. f. Psychiat. u. Neurol. **25**:565, 1909.

8. Claude, H., and Cuel, J.: Notes anatomo-cliniques sur trois cas de délire aigu, Encéphale **22**:628, 1927.

9. Josephy, H.: Beiträge zur Histopathologie der Dementia praecox, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:391, 1923.

10. Braunmühl, A.: Ueber Gehirnbefunde bei schweren Erregungszuständen, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:163, 1928; Ueber Gehirnveränderungen bei puerperaler Eklampsie und ihre Entstehung durch Kreislaufstörungen, ibid. **117**:698, 1928.

severe excitement and collapse, which reflexly bring about lability in the cerebral vasomotor system. On the basis of these observations Spielmeyer [11] rejected the concept of a primary anatomic process as underlying the acute disorder by stating: "The cerebral death in catatonia is the result of a circulatory collapse . . . and has no direct bearing on the disease itself."

REPORT OF A CASE

History.—M. C., a white woman aged 20, was admitted to the hospital on Jan. 28, 1936. The family history contained several instances of neurosis and unstable psychopathic personality. The childhood of the patient was marked by instability, temper tantrums and neuropathic traits of enuresis, thumb sucking, nail biting and talking during sleep. The menses began at the age of 15 and were always irregular. The patient was of superior intelligence but was innately cold, irritable and lacking balance.

The illness under consideration had begun nine months prior to admission, when she gradually became tense and restless and felt inferior to others. This was followed by acute periods of surly, negativistic, uncommunicative behavior alternating with noisy, destructive episodes in response to auditory and visual hallucinations. During these nine months she had but a single scanty menstrual period lasting one day.

Examination on Admission.—The patient was poorly nourished and asthenic. The pulse was feeble and the rate was 88 per minute; the cardiac sounds were faint, and the blood pressure was 105 systolic and 58 diastolic. The extremities were cool and moist, and the feet were of a moderate reddish blue. There were some rigidity of the extremities, generalized hyporeflexia and slight vertigo, but no other neurologic findings. The urine was normal. Examination of the blood revealed 4,310,000 red cells and 5,300 white cells per cubic millimeter; the hemoglobin concentration was 85 per cent; the Kahn reaction of the blood was negative.

The patient was restless, irritable and uncommunicative; her psychomotor activities were jerky and erratic and her responses desultory and irrelevant. She expressed vague, unelaborated ideas of alien control, but no other delusions or hallucinations. She displayed no interest in her surroundings, spending her time staring blankly into space and mumbling to herself. Her condition was diagnosed as schizophrenia of the catatonic type.

Course.—In the first three months of hospitalization her condition fluctuated between episodes of acute excitement and periods of apathetic inactivity. During the following months she showed increasing apathy and seclusiveness. Ambivalence, mannerisms and attitudinizing became prominent, and it was apparent that the psychosis was running a decompensating course. The patient refused food and lost weight, necessitating mechanical feeding during the greater part of her hospitalization.

The fatal episode occurred on the morning of Oct. 19, 1936. Nothing unusual was noted in the patient's behavior until then, although there had been an increased irritability during the preceding few days. She was given 1 pint (470 cc.) of eggnog by tube at 8:15 a. m., the procedure being accomplished without struggle or complications. Twenty minutes later she vomited and became restless, running aimlessly about the ward and appearing anxious and frightened. She seemed to

11. Spielmeyer, W.: Kreislaufstörungen und Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:536, 1930.

realize that some serious complication had occurred, saying: "It is all my own fault. I let myself get into this condition, and I don't have any one to blame for it but myself." After this she no longer responded to questions or commands but struggled constantly to rise from bed and resume her aimless flight around the ward. Her skin was ashen grayish blue and the lips and nail beds deeply cyanotic, and she appeared to be in shock and collapse.

Within fifteen minutes she lapsed into stupor, but still responded to painful stimuli by withdrawing both sides of the mouth. The respiration became shallow; the pulse rate was 100 and irregular, feeble and frequently fading; the blood pressure was 120 systolic and 80 diastolic. The rectal temperature was 102.6 F. There was moderate dissociation of the extraocular movements; the pupils were moderately dilated, reacting little to light, and there was hippus. There was no stiffness of the neck. The extremities were moderately rigid; all tendon reflexes were equal and hyperactive; the abdominal reflexes were normal. The Babinski response was suggestively positive bilaterally, but no other pathologic reflexes were elicited. There were generalized myoclonic twitchings, especially prominent in the shoulder girdle. The urine contained a trace of sugar. A blood count revealed 12,600 white cells. The carbon dioxide–combining power of the blood was 53 volumes per cent.

The application of external heat was followed by slight general improvement. At 1 p. m. examination of the blood revealed 5,240,000 red cells, 13,600 white cells and a hemoglobin concentration of 85 per cent. The cerebrospinal fluid was under increased pressure; it was cloudy and slightly blood tinged, the blood being apparently not due to operative trauma. The fluid contained 3,200 red blood cells per cubic millimeter; the reaction for globulin was 3 plus; the Kahn, the colloidal gold and the mastic reaction were negative.

Throughout the afternoon the patient remained in coma and had occasional periods of restlessness, during which she rolled about in bed, moving all extremities. The pupils were moderately dilated and responded to light. The right arm was semiflexed and moderately hypertonic and manifested occasional tremors.

On the morning of October 20 rigidity of the neck and positive Brudzinski and Kernig signs were noted. The cyanosis, which was constantly present, fluctuated periodically in intensity, and there were corresponding changes in the strength of the cardiac action. At 10 a. m. there was a convulsive seizure of the jacksonian type, involving the right arm and fingers, followed at short intervals by a series of about twenty-five convulsive attacks. Some of them involved the right arm or the right arm and leg, while others were generalized but apparently initiated by twitchings of the right side of the body. One hour later, the seizures became severe and continuous. The convulsions were controlled with soluble phenobarbital U. S. P. (sodium phenobarbital), but there was no improvement in the general condition, the pulse becoming weak and thready and the respiration rapid and labored. Supportive treatment and continuous hypodermoclysis were administered. In the afternoon the respiratory rate rose to 44 per minute, the pulse became barely perceptible, with a rate of 130 per minute, and the rectal temperature rose to 105.4 F. Another examination of the cerebrospinal fluid revealed a pressure of 110 mm. of water, 368 red blood cells per cubic millimeter and 109 mg. of sugar per hundred cubic centimeters, but no other significant findings. A simultaneous determination of the sugar content of the blood revealed 117 mg. per hundred cubic centimeters. The hemoglobin concentration of the blood was 100 per cent (Sahli); there were 6,870,000 red cells and 23,400 white cells, with 93 per cent polymorphonuclear leukocytes, 5 per cent lymphocytes and 2 per cent monocytes. The urine contained a trace of albumin.

On the morning of October 21 the patient rallied somewhat, but still remained in deep coma. The pulse became slower and stronger (the rate being 70 to 80 per minute), the respiratory rate fell and the temperature varied between 101 and 103 F. The white blood cell count fell to 11,200. However, in the late afternoon the physical condition became worse. The cardiac action became feeble and irregular with occasional extrasystoles, suggesting auricular fibrillation. The patient died at 5 a. m. on October 22, approximately sixty-eight and one-half hours after the onset of the fatal episode.

Necropsy.—Examination forty-five minutes after death showed the general nutrition of the body to be fair. The essential changes in the internal organs were: right-sided purulent bronchopneumonia, acute pulmonary congestion, edema and focal hemorrhages; beginning acute purulent gastritis, with ulcerative involvement of the fundus, edema and petechial hemorrhages in the mucosa and submucosa; subepicardial fatty infiltration; lipoidosis of the liver; generalized acute passive congestion; generalized lymphoid hyperplasia; hypoplasia of the heart and aorta, and advanced fatty atrophy of the thymus. The bone marrow was congested and exhausted to a degree usually considered incompatible with life.

The brain weighed 1,455 Gm. and showed evidence of swelling. The dura and leptomeninges were stretched and congested. The blood vessels of the base and of the convexity were delicate; they were engorged but not thrombosed. The brain substance in general was firm, and its surface was dry; the convolutions were flattened and the sulci obliterated. However, the cortex of the temporal lobes was severely necrotic, friable and blood tinged. Coronal sections disclosed throughout both hemispheres a hyperemic and mottled cortex, studded with sharply defined grayish necrotic, partly hemorrhagic foci, varying greatly in size. The most extensive softenings occupied the cortex of both temporal lobes, including the nuclei amygdalae and the cornu ammonis, both insulae and the cingulate and inferior gyri of both frontal lobes. The rest of the frontal and the entire parietal and occipital cortex contained numerous small discrete lesions. The white matter was edematous, containing occasional petechial hemorrhages but no distinct foci. The ventricles, the ependyma and the choroid plexus were normal. The structures of the basal ganglia, brain stem and spinal cord (of which only a segment of the thoracic portion was available) were well outlined but were moderately hyperemic. In the cerebellum there were marked congestion and scattered petechial hemorrhages.

MICROSCOPIC OBSERVATIONS

Leptomeninges: The pia-arachnoid was congested and contained scattered hemorrhages, lymphocytes and histiocytes but was not thickened. The blood vessels were greatly distended and engorged, but were otherwise normal.

Cortex: The entire cerebral gray matter was "moth eaten" by countless necrotic lesions, which interrupted its cytoarchitecture. These varied in size from small circular foci restricted to a single layer (fig. 1) to large softenings involving one or several convolutions (figs. 2-4). They were circular or triangular, frequently coalescing and thus assuming pseudolaminar patterns. The base of the triangular lesions was usually nearest the surface, with the apex pointing downward. The lesions most commonly involved the crests of the convolutions and contiguous portions of the adjacent gyri. The majority of the small and laminar foci occurred in the third layer, the larger lesions involving also the neighboring layers. In the large softenings almost the entire width of the cortex was involved, leaving intact only scattered islands of parenchyma or a narrow band

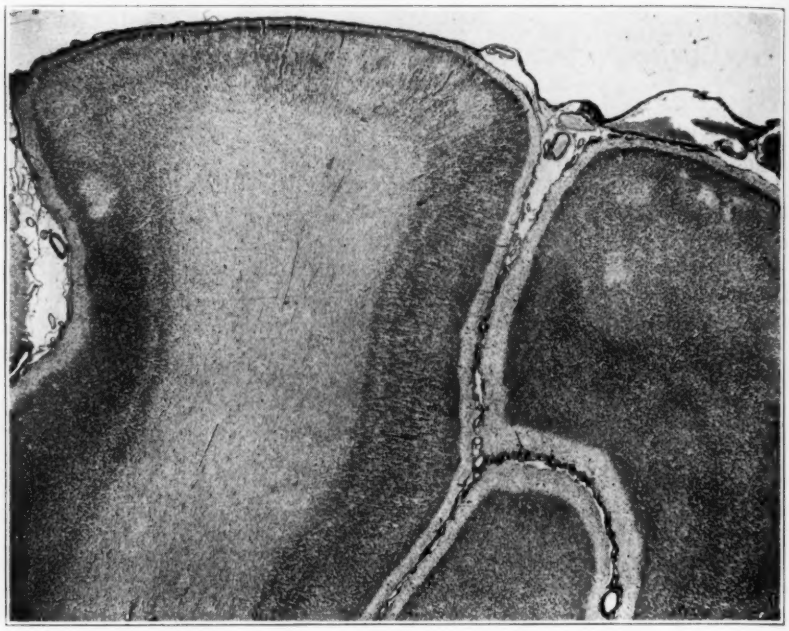

Fig. 1.—Multiple discrete and coalescing ischemic lesions in the cortex of the left frontal lobe, chiefly involving the third layer. Nissl stain; Zeiss planar lens, 75 mm.

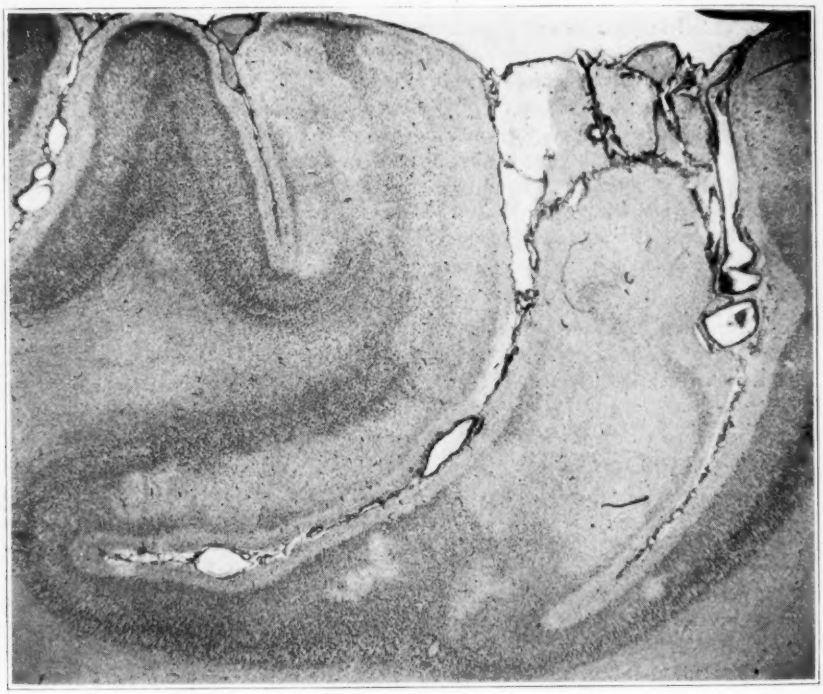

Fig. 2.—Extensive lesions destroying several convolutions of the cingulate gyrus in the left frontal lobe. Nissl stain; Zeiss planar lens, 75 mm.

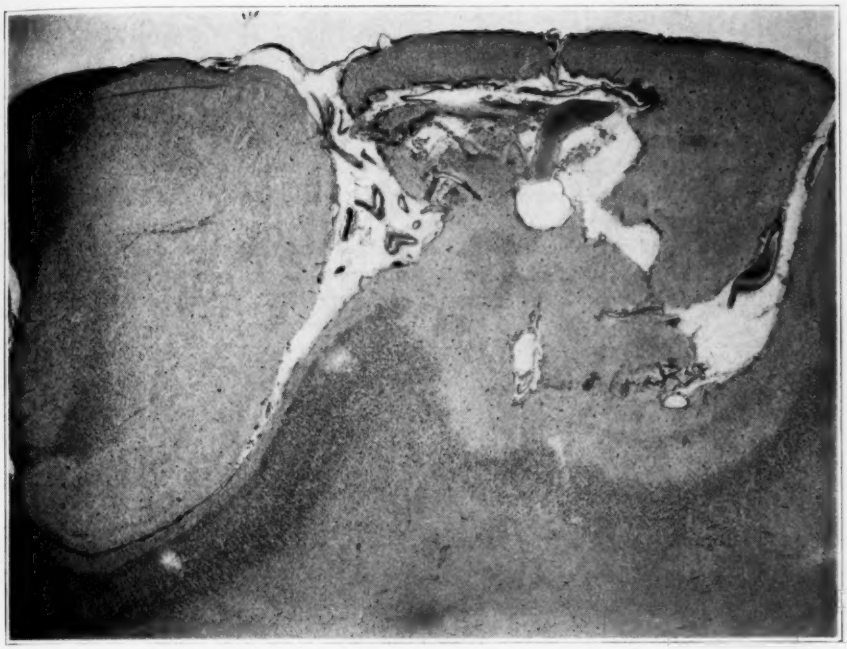

Fig. 3.—Similar extensive involvement of the cortex in the cingulate gyrus of the right frontal lobe. Nissl stain; Zeiss planar lens, 75 mm.

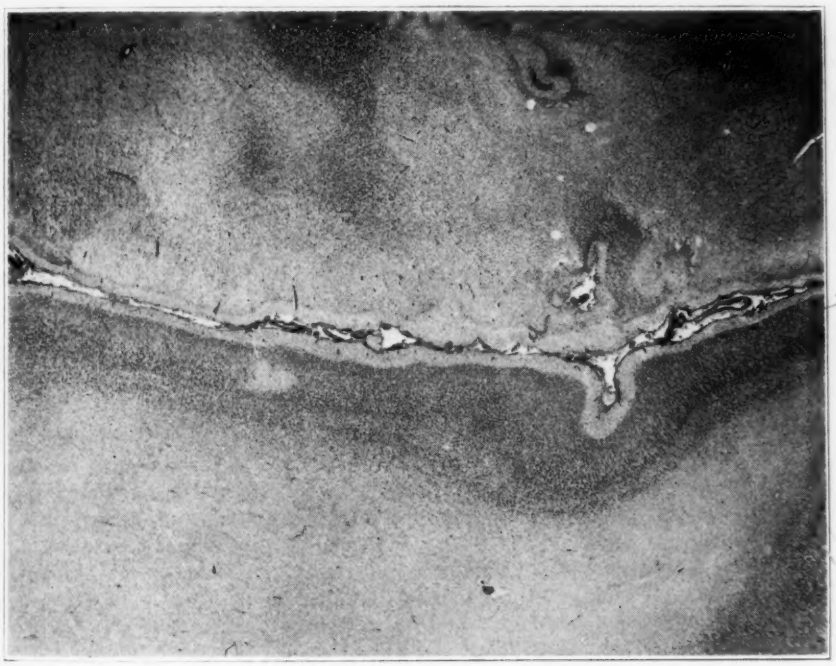

Fig. 4.—Severe destruction of the cortex in the roof of the left sylvian fissure, with isolated focus in the floor of the latter. Nissl stain; Zeiss planar lens, 75 mm.

of lamina VI bordering on the white matter. In the cornu ammonis there was selective destruction of the end plate and Sommer's sector, the resistant part being preserved.

The histologic details were uniform in all the lesions. In Nissl preparations (fig. 5) the tissue was rarefied and stained pale green. The interstitial Nissl gray was crumbling and granular, and the neurons and glia were greatly reduced. The remaining structures consisted of shadows of cells and dendrites and of shrunken pale "ischemic" neurons with pyknotic nuclei surrounded by numerous incrusta-

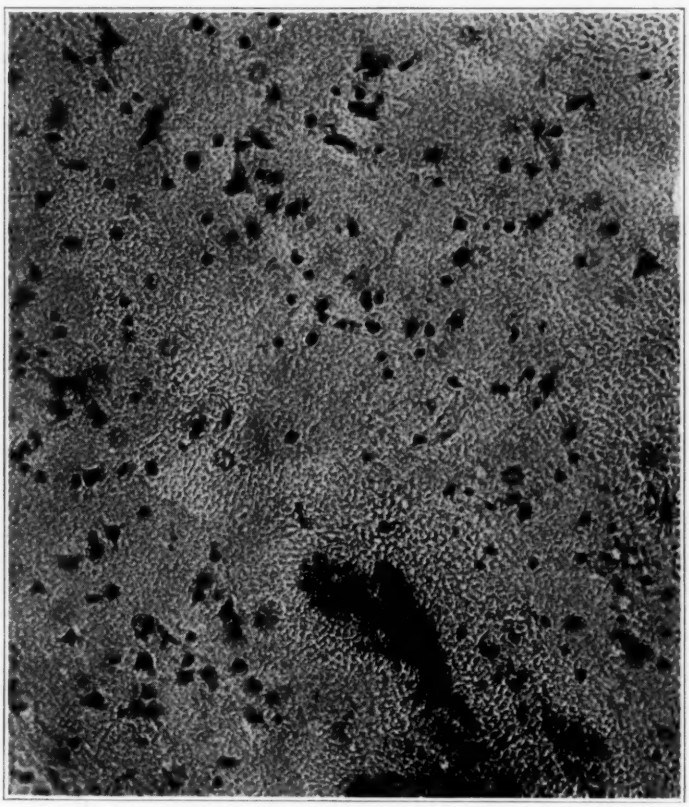

Fig. 5.—Ischemic degeneration of the neurons, necrosis of the Nissl gray and scattered hemorrhages within a cortical lesion. Nissl stain; Zeiss objective × 20; ocular no. 2.

tions. In silver preparations the neurofibrils showed severe granular disintegration. The glia was karyorrhectic; there was occasional perivascular proliferation of microglia and gitter cells but no other progressive phenomena. The myelin sheaths and axis-cylinders of the cortex were largely destroyed. In sections stained with scarlet red scant lipoid deposits were seen in the perivascular spaces. In many of the foci the small blood vessels and capillaries were conspicuous by congestion, stasis and perivascular migration of leukocytes. In others, on the contrary, the vessels were poorly visible. This picture of alternating hyperemia

and ischemia was especially well demonstrated with the Weigert stain for fibrin, which, however, disclosed no thrombi. Small perivascular ring and diffuse hemorrhages were frequent. There was no iron. The walls of the blood vessels were normal, with the exception of slight swelling of the endothelium. Some of the parenchymatous lesions showed incomplete necrosis, such as paling (*Erbleichung*) and beginning ischemia of the neurons. In the border zones of the lesions there was no evident cellular reduction, but the neurons disclosed nonspecific changes of swelling, vacuolation and beginning ischemia, not associated with any glial or mesodermal reaction.

In the gray matter between the lesions the cytoarchitecture was preserved, but the neurons were largely "sclerotic," with honeycomb appearance of the cyto-

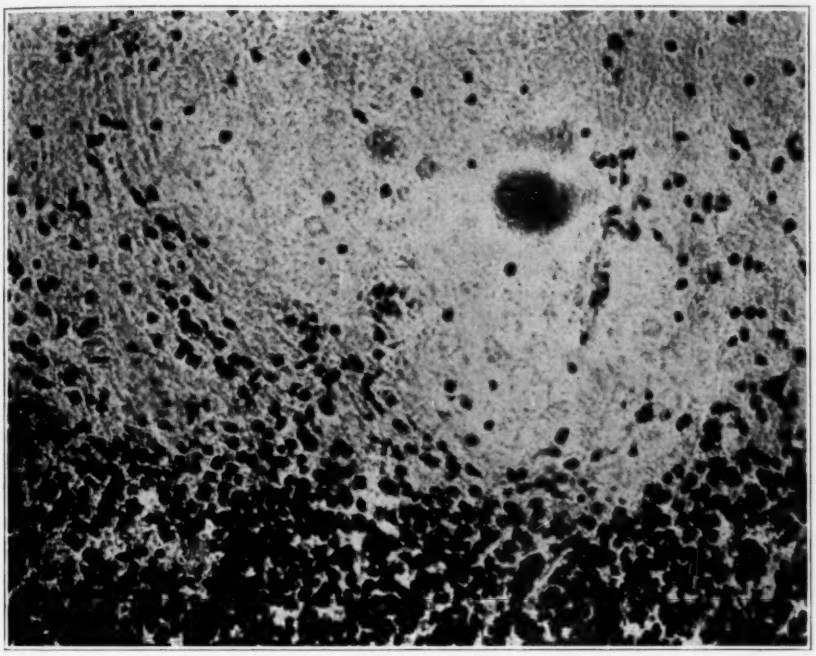

Fig. 6.—Necrosis, hemorrhages and glial shrubberies in the molecular layer and degeneration of the Purkinje cells of the cerebellum. Nissl stain; Zeiss objective × 20; ocular no. 2.

plasm (*wabige Degeneration*) and corkscrew-like processes, but without any increased lipoid content. Nissl's acute swelling and severe degeneration were rare. The glia and blood vessels were normal.

White Matter: There were scattered perivascular hemorrhages and accumulations of gitter cells, containing blood pigment and fat; diffuse swelling of the oligodendroglia and rarefaction of the myelin, largely due to edema.

Basal Ganglia and Brain Stem: In the claustrum, thalamus, hypothalamus, subthalamic body and quadrigeminal plate there were occasional small necrotic foci and petechial hemorrhages.

Cerebellum: The gray matter was severely involved (fig. 6). In the molecular layer there were numerous ischemic and hemorrhagic necrotic foci and glial

shrubberies. The Purkinje cells were reduced, those remaining showing Spielmeyer's "homogenizing disorder." In the granular layer the lesions were less numerous. The dentate nucleus was normal, and in the white matter there was moderate irritation of the glia.

Comment.—The patient presented the ordinary clinical features of schizophrenia. The diagnosis was based on the asthenic-schizoid constitution and on the development of the psychosis, which progressed rapidly from acute catatonic episodes to hebephrenic deterioration. The clinical studies offered no definite explanation for the occurrence of the fatal disorder. Some significance may be ascribed to the constitutional vasomotor instability, evidenced by general circulatory deficiency, acrocyanosis, hypotension and menstrual irregularities, although this is by no means uncommon in schizophrenia. The acute episode began with characteristic dramatic suddenness, but the initial phase of panic, anxiety and motor agitation was extremely brief, lasting no longer than fifteen minutes, and may be regarded as a miniature of the period of excitement described in the literature, which usually lasts for several days or weeks. This brief phase of excitement was followed by complete collapse, obviously of central origin, characterized by coma, cyanosis, hyperthermia, respiratory and circulatory failure and vague neurologic signs. The findings in the cerebrospinal fluid indicated subarachnoid hemorrhage. After the initial shock was partially relieved, the clinical picture was dominated by signs of meningeal and cortical irritation, the latter being manifested by jacksonian and generalized paroxysmal convulsive attacks. Although the convulsions were controlled, the coma persisted, and death ensued approximately sixty-eight and one-half hours after the onset.

The hematologic findings were of particular interest and consisted of a marked increase in the erythrocyte count, a moderately elevated concentration of hemoglobin and leukocytosis. These findings indicated an increased viscosity of the blood, which did not appear to be due to dehydration, since the patient was receiving sufficient fluids. It suggested relative polycythemia, which, however, could not be definitely established in the absence of a determination of the blood volume. There were no available data regarding the presence of reticulocytosis, which would indicate erythropoietic activity (Jahn and Greving). On the contrary, necropsy disclosed signs of exhaustion of the bone marrow.

Pathoanatomically, the most striking feature was the presence of numerous softenings in the cortex of the cerebrum and of the cerebellum, although there was some evidence of brain swelling. The lesions were characterized by a patchy focal distribution, with selective involvement of "vulnerable" regions (cornu ammonis, cerebellum), and histologically by ischemic and hemorrhagic necrosis. These features indicated that the lesions were of a vascularly determined origin, although there were no demonstrable structural changes in the related meningeal and cortical vessels. Within the lesions areas of capillary stasis and hemorrhage by diapedesis alternated with areas of anemia. All the lesions were devoid of gliomesodermal reaction, suggesting necrosis of the coagulation type. In addition, there were diffuse sclerosis and honeycombed degeneration of the neurons throughout the cortex.

In the organs of the body there were bronchopneumonia and acute gastritis, both conditions being apparently terminal.

GENERAL COMMENT

This case is unique in that the pathoanatomic picture offers an adequate explanation for the otherwise mysterious "brain death." The clinical features suggest a cerebral disorder of a vascular type. The

symptoms may be regarded as an exaggeration of the triad of "vital endogenous" anxiety, confusional states and epileptiform attacks which, according to Krapf,[12] is pathognomonic of cerebral circulatory disorders. Since it is evident that the cerebral lesions have a vascular pathogenesis, this clinical conception is substantiated by the pathoanatomic findings.

The simultaneous involvement of different parts of the brain and the absence of organic changes in the blood vessels suggest that the lesions are produced by a "functional" disturbance of the circulation in the sense accepted by Braunmühl and Spielmeyer. However, although this theory offers a pathogenetic explanation for the lesions, it fails to consider the etiologic mechanisms responsible for the circulatory disturbances. Braunmühl and Spielmeyer dismissed these circulatory disturbances as purely secondary phenomena and expressed the belief that they are reflexly produced by the mental excitement. However, it is difficult to apply this explanation to cases such as ours, in which a minimum of excitement is present and the predominant feature is collapse. Such profound changes in the entire organism must have a fundamental cause and cannot be interpreted as a mere symptomatic expression of the excitement.

This problem may be more adequately understood in the light of the recent observations by Stauder and by Jahn and Greving. These authors attributed the fatal disorder to the general collapse of the peripheral circulation, as evidenced by the marked acrocyanosis, spontaneous hematomas, relative polycythemia and erythropoietic activity of the bone marrow. It is reasonable to believe that a collapse similar to that of the peripheral circulation may occur in the cerebral capillary system. Guttmann,[13] in discussing mental disorder associated with Raynaud's syndrome, migraine and other vasomotor neuroses, expressed the opinion that: "Something similar in kind to what can be seen in the peripheral vessels may occur in the brain, viz., vasomotor disturbances of some description." However, up to the present time this association of peripheral and central vascular phenomena has not been verified pathoanatomically by a demonstration of circulatory disturbances in the central nervous system. In our case just this concomitant occurrence of vasomotor disturbances in the circulation of the brain and in that of the periphery supplies the necessary proof. It is possible that the same circulatory mechanism may be responsible for the occurrence of brain swelling, for, according to Krapf, "circulatory troubles will be amongst the most important stimuli to provoke *Hirnschwellung.*"

The question arises as to the relationship between "brain death" and the preexisting schizophrenic process, in which it frequently occurs. Whether the acute disorder is to be regarded as a separate nosologic entity, an exacerbation of the schizophrenic process or purely a complication of the preceding psychosis depends on the attitude of the individual investigator. It does not appear probable that schizophrenia has a direct causal relationship to the acute disorder, as sudden brain

12. Krapf, E.: The Circulatory Factor in the Pathogenesis of Mental Disorder, J. Ment. Sc. **83**:534, 1937.

13. Guttmann, E.: Psychological Implications of Functional Circulatory Disorder, J. Ment. Sc. **83**:542, 1937.

death occurs in other psychoses and in nonpsychotic persons. Furthermore, no specific pathologic picture described for schizophrenia has met with general acceptance. In our case the so-called chronic sclerotic changes in the cortical neurons constituted doubtful evidence of Josephy's criteria for an anatomic substratum of schizophrenia. Such changes are commonly encountered in acute conditions and in this case may be ascribed to the general circulatory disturbance.

In our case the vascular source of the cerebral lesions indicated that we were dealing with a complication, rather than a direct result, of the schizophrenic psychosis. However, as stated before, we cannot agree with Spielmeyer's contention that these circulatory disturbances are purely symptomatic manifestations of the excitement. It seems more likely that a certain constitutional predisposition must be assumed in such cases, in view of the general phenomena of vasomotor instability. Whether this is to be understood as an inherited hemorrhagic diathesis (Stauder), as histamine intoxication resulting from disturbed protein metabolism in the asthenic-schizoid constitution (Jahn and Greving [4]) or as a manifestation of an "inadequate autonomic nervous system with clumsy adaptive responses to changed conditions" (Minski [14]) requires further investigation. The fact that such acute disorders are prone to occur in schizophrenia may be ascribed to the vasomotor lability characteristic of this psychosis. It is reasonable to assume that in a certain group of cases of schizophrenia an intense expression of this lability would precipitate complete vasomotor collapse with fatal termination.

SUMMARY

The hitherto unexplained disorder of "sudden brain death" is illustrated in a case of schizophrenia with the unique pathoanatomic picture of widespread cerebral vascular lesions.

Pathogenetically, the character of the lesions suggests a functional disturbance of the cerebral circulation which is correlated with similar signs of vasomotor collapse in the peripheral circulation.

Etiologically, the fatal disorder is attributed to a constitutional vasomotor lability commonly seen in schizophrenia and not directly to the psychosis.

14. Minski, L.: A Note on Some Vasomotor Disturbances in Schizophrenia, J. Ment. Sc. **83**:437, 1937.

HEMIBALLISMUS

A Clinicopathologic Study

FREDERICK P. MOERSCH, M.D., AND JAMES W. KERNOHAN, M.D.,
ROCHESTER, MINN.

According to Oppenheim,[1] the term "hemiballismus" was first employed by Kussmaul [2] to describe a certain type of hemichorea which Mitchell [3] and Charcot [4] previously had referred to as "posthemiplegic chorea," a term which never had the approval of Gowers.[5] At about the same time (1871) Hammond [6] introduced into the neurologic literature the term "athetosis." It is evident that these early writers recognized a difference between the movement patterns of tremor chorea and athetosis.

In spite of the fact that these disorders of movement could be distinguished clinically, it was assumed that they represented different methods of motor expression and were the result of a diffuse lesion involving part or the whole of the basal ganglia rather than of any specific and focal lesion in these structures. Bonhoeffer [7] was one of the first to attribute chorea definitely to a subthalamic lesion, although as early as 1882 this suggestion had been made by other writers. After the appearance of the reports of von Economo [8] and Fischer,[9] in 1910

Read at the Sixty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 2, 1938.

From the Section on Neurology (Dr. Moersch) and the Section on Surgical Pathology (Dr. Kernohan), the Mayo Clinic.

1. Oppenheim, H.: Lehrbuch der Nervenkrankheiten für Aerzte und Studierende, ed. 7, Berlin, S. Karger, 1923, pp. 1056-1077.

2. We have been unable to verify this reference. Priority in the use of the term also has been attributed to von Economo, Fischer and Jakob. It is certain that the term was employed prior to the publication of Jakob's contributions.

3. Mitchell, S. W.: Post-Paralytic Chorea, Am. J. M. Sc. **68**:342-352 (Oct.) 1874.

4. Charcot, J. M.: Lectures on the Diseases of the Nervous System, London, New Sydenham Society, 1877, vol. 3.

5. Gowers, W. R.: On "Athetosis" and Post-Hemiplegic Disorders of Movement, Med.-Chir. Tr., London **59**:271-325, 1876.

6. Hammond, W.: De l'athétose, Arch. gén. de méd. **2**:329-335 (Sept.) 1871.

7. Bonhoeffer, K.: Ein Beitrag zur Localisation der choreatischen Bewegungen, Monatschr. f. Psychiat. u. Neurol. **1**:6-41, 1897.

8. von Economo, K.: Beitrag zur Kasuistik und zur Erklärung der posthemiplegischen Chorea, Wien. klin. Wchnschr. **23**:429-431 (March 24) 1910.

9. Fischer, O.: Zur Frage der anatomischen Grundlage der Athétose double und der posthemiplegischen Bewegungsstörung überhaupt, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:463-486, 1911.

and 1911 respectively, renewed attention was given to the subject of hemichorea. Fischer made a careful clinicopathologic study of chorea and athetosis. He was able to find only 5 cases of hemichorea previously studied anatomically, to which he added his own case, an excellent example of this condition. It remained, however, for Jakob [10] in 1923 to postulate definitely that the syndrome of hemichorea, or hemiballismus, is attributable to a lesion of the corpus Luysi and that an additional cerebral component is not essential to the production of the disorder of movement. This is contrary to the view maintained by Wilson [11] and other writers. It is noteworthy that in spite of the interest shown by Mitchell [3] and by Hammond [6] in the study of disorders of movement, only three studies on hemichorea by American authors are referred to by writers on this subject, namely, that of Canfield and Putnam [12] in 1884, that of Lloyd and Winkelman,[13] in 1925 and that of Weil [14] in 1928.

One of the next important contributions to the subject of hemichorea was made by Martin [15] in 1927. He was able to collect from the literature some 20 cases of hemichorea, 12 of which he found to be of scientific value. He did not include the cases studied by Fischer [9] but did include Fischer's own case. To this series Martin added 1 case of his own. On the basis of his studies he postulated a clearly defined syndrome of the corpus Luysi. In an excellent later contribution Martin and Alcock [16] recorded some additional observations and expressed agreement with other writers that hypotonia, vegetative symptoms and psychic changes, although rather constantly present in such cases, are neighborhood symptoms rather than specific symptoms resulting from a lesion of the corpus Luysi.

As a result of these and other clinicopathologic studies it is now recognized fairly well that there is a syndrome of the corpus Luysi, which is designated as hemichorea, or, as some prefer to call it, hemiballismus, the terms being used interchangeably. There remains, however, considerable controversy as to the exact anatomic basis for the disorder of movement which characterizes this condition. The most frequent sites postulated for the lesion producing the syndrome are the cortex, the thalamus, the cerebellothalamic tracts and the corpus

10. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923, pp. 183-225.

11. Wilson, S. A. K.: Die Pathogenese der unwillkürlichen Bewegungen mit besonderer Berücksichtigung der Pathologie und Pathogenese der Chorea, Deutsche Ztschr. f. Nervenh. **108**:4-38 (March) 1929.

12. Canfield, R. M., and Putnam, J. J.: A Case of Acute Hemiplegic Chorea, with Autopsy and Remarks, Boston M. & S. J. **111**:220-223 (Sept. 14) 1884.

13. Lloyd, J. H., and Winkelman, N. W.: A Case of Acute Posthemiplegic Choreiform Movements on the Unparalyzed Side: Study of the Basal Ganglia, Am. J. M. Sc. **169**:247-253 (Feb.) 1925.

14. Weil, A.: A Contribution to the Pathology of Hemichorea, Brain **51**:36-45 (March) 1928.

15. Martin, J. P.: Hemichorea Resulting from a Local Lesion of the Brain (Syndrome of the Body of Luys), Brain **50**:637-651 (Oct.) 1927.

16. Martin, J. P., and Alcock, N. S.: Hemichorea Associated with a Lesion of the Corpus Luysii, Brain **57**:504-516 (Dec.) 1934.

striatum. Wilson,[11] Wulff [17] and others maintained that a cortical component must be present to produce the uncontrolled movements and that a single isolated anatomic lesion either in the corpus striatum or elsewhere cannot cause choreic movements. Ranson [18] has avoided making a specific statement as to the possible site of the anatomic lesion, maintaining that the problem is not too clear and that the syndrome is probably the result of disruption of coordinating impulses coming from the thalamus, the corpus striatum and the pyramidal tracts before they descend in the cerebral peduncles. Although there is no unanimity of opinion regarding all the factors pertaining to the production of choreic symptoms, certain facts appear to be established. Thus, Jakob [10] described the corpus Luysi as a regulator of movement producing a synergy of movements of the contralateral side of the body. Pelnář and Sikl [19] have expressed this idea in slightly different terms, stating that the corpus Luysi acts as a regulator of movement tone in contradistinction to the pallidum which regulates permanent tone. Although many of the reported cases of hemichorea have included a lesion of the cerebrum in addition to a lesion of the corpus Luysi, it is by no means certain that such a combination of lesions is necessary to the production of hemichorea. It does appear essential for the production of choreic movements that the following structures be functionally intact: the red nucleus, the substantia nigra and the pyramidal tracts. In spite of the present knowledge regarding the situation of the lesion producing hemichorea, it remains a debatable question whether the movements are the result of an irritative or of a destructive process. Although laboratory experimentation has not been particularly helpful in throwing light on this phase of the subject, the consensus is that there must be a destructive lesion in or near the corpus Luysi which controls the impulses producing the choreic movements. As has been pointed out by Balthasar,[20] every lesion of the corpus Luysi does not produce hemichorea; this is true especially if the lesion is extensive and causes interruption of the pyramidal tracts.

Early writers referred to the corpus Luysi as having certain vegetative functions. Von Sántha,[21] Wulff,[17] Martin [15] and others pointed out that these symptoms are not functions of the corpus Luysi but result from a disturbance in adjacent groups of cells. In 1932, von Sántha [21] as a result of careful studies of serial sections of the corpus Luysi came to the conclusion that there is a somatotropic relation between the cellular

17. Wulff, H.: Corpus Luysi und das hemiballistische Syndrom, Acta psychiat. et neurol. **7**:999-1019, 1932.

18. Ranson, S. W.: The Anatomy of the Nervous System, ed. 5, Philadelphia, W. B. Saunders Company, 1934, p. 222.

19. Pelnář, J., and Sikl, H.: L'hémiballisme, le ballisme aigu et le corps de Luys, Rev. neurol. **2**:328-331 (Sept.) 1929.

20. Balthasar, K.: Ueber das Syndrom des Corpus Luys an Hand eines anatomisch untersuchten Falles von Hemiballismus, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:702-720, 1930.

21. von Sántha, K.: Hemiballismus und Corpus Luysi (Anatomische und pathophysiologische Beiträge zur Frage des Hemiballismus nebst Versuch einer somatotopischen Lokalisation im Corpus Luysi), Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:321-342, 1932.

structure of this body and the site of the choreic movements, the oral pole of the nucleus corresponding to the face, the middle portion to the arm and trunk and the caudal pole to the lower extremity. Martin [15] and, recently, Juba and Rakonitz [22] have substantiated these observations. Cases of hemiballismus are on record in which the face or one limb of the affected side has been spared. This is thought to be the result of the cellular arrangement in the corpus Luysi and the related blood supply, which, as pointed out by Hampel,[23] is derived from three arteries: a branch of the posterior cerebral artery, a choroidal artery and a branch of the posterior communicating artery. As a result of this excellent blood supply complete destruction of the corpus Luysi is rare.

The terms hemichorea and hemiballismus have been used interchangeably since the introduction of the latter term. Some writers have suggested reserving the term hemiballismus to designate the syndrome of the corpus Luysi in distinction to hemichorea occurring in childhood. They have concluded that the suddenness of the cerebral insult may lead to the difference in the movements, an acute vascular insult producing the violent hemiballistic movements and a more insidious, inflammatory lesion producing the less violent hemichoreic movements. A review of the literature militates against such a conception. Martin and others concluded, as the result of their observations (including cinematographic studies), that there is no fundamental difference in the movements and that what difference does occur is one of degree and situation and not of kind.

REPORT OF A CASE

A man aged 65 had been in good health until Aug. 16, 1937, when he noticed transient weakness and a sensation of numbness over his left side. He recovered within twenty minutes and in the ensuing days seemed well. On August 24 he suddenly became confused, and within an hour coarse choreiform movements of the left arm and, to a lesser degree, of the left leg occurred. There was constant grimacing of the left side of the face. He had not been in coma and remained mentally clear. In the following few days the disorder of movement became more severe; the speech became explosive, and there were constant grimacing and contorted movements of the mouth and tongue, so that the speech became unintelligible. Movements of the left arm and leg became exceedingly violent, and the patient would strike himself or those about him very forcibly; these movements were so gross and explosive that they hardly could be termed choreiform. He continued to understand what was said to him, although he appeared mentally clouded.

Aside from these violent choreiform movements, which affected the entire left side, neurologic examination revealed little of special consequence. As far as could be determined, there was no motor weakness. Sensation was intact. The deep reflexes were present and were about equal on the two sides. There was no evidence of any disturbance of the pyramidal tracts. Examination of the spinal

22. Juba, A., and Rakonitz, J.: Ueber einen Fall von Hemiballismus (Beitrag zur Somatotopie des Corpus Luysi), Arch. f. Psychiat. **106**:629-642, 1937.

23. Hampel, E.: Hemiballismus auf luischer Grundlage: Beitrag zur pathologischen Anatomie und Pathogenese des Hemiballismus, Deutsche Ztschr. f. Nervenh. **141**:77-96 (July) 1936.

fluid gave entirely normal results. It was exceedingly difficult to control the choreiform movements even with the use of morphine, hyoscine or magnesium sulfate intramuscularly. Gradually the patient became exhausted, and there was some lessening of the violence of the movements. On September 12 the temperature mounted to 103 F. (39.4 C.), and signs of bronchopneumonia developed. During the ensuing days the disorder of movement lessened, but the patient was unable to talk and was confused and disoriented. He died on September 18,

Fig. 1.—Two miliary infarcts in the corpus Luysi on the left side. The infarcts are at the caudal and medial portion of the body.

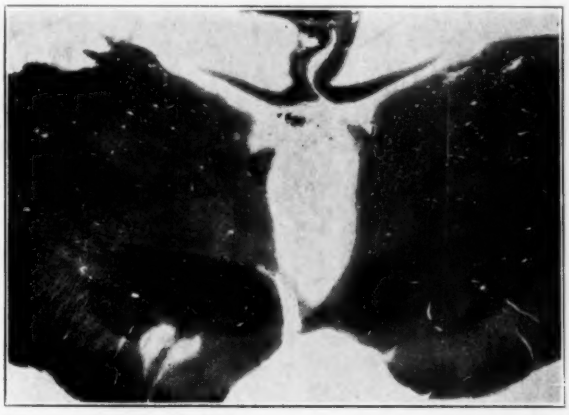

Fig. 2.—Section showing the infarcts and their relation to the substantia nigra, the cerebrospinal tracts and the red nucleus (Weigert's stain).

twenty-six days after the onset of the choreiform movements and thirty-four days after the onset of the first clinical symptom.

Necropsy.—There was bilateral bronchopneumonia, most severe in the lower lobes of the lungs. There was also a moderate degree of bronchiectasis. The gastric mucosa was much congested, but ulceration was not present. Arteriosclerosis of the aorta, the coronary artery and other large arteries was estimated as of grade 2 (on the basis of 1 to 4). No other lesion of any significance was

observed in the organs of the thorax or abdomen. There was no gross abnormality in the brain and no atrophy of the cortex or dilatation of the ventricles. There was arteriosclerosis, grade 2, of the vessels of the circle of Willis. Coronal section of the brain showed two small cystlike infarcts in the left subthalamic body (fig. 1). There was an infarct about 1 mm. in diameter in the pons, directly beneath the pia and near the point of entrance of the left fifth nerve. No other infarct was present in the central nervous system, and there was no hemorrhage or other lesion.

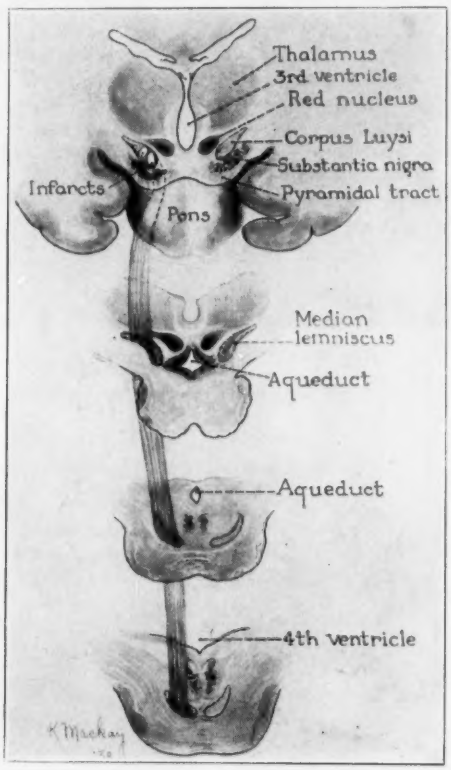

Fig. 3.—Illustration of the destruction of fibers originating in the subthalamic body, as accurately as could be determined.

Histologic Examination.—Sections made through the ~~left~~ Right (see p 1270) subthalamic body gave evidence of two small infarcts (fig. 2). During the process of cutting and handling the tissue most of the cells in these lesions had fallen out, but some compound granular corpuscles remained in the walls of the infarcts. There were no inflammatory cells or granules of blood pigment in the tissue surrounding the infarcts, and there was little glial reaction around the lesions. Approximately half of the corpus Luysi had been destroyed; the lesion had included the inferior and medial portion and was situated at the caudal end of the nucleus but had not extended into the substantia nigra or the red nucleus and did not involve the corticospinal fibers. The subthalamic cells superior and lateral to the infarcts

were normal; not even satellitosis was present. Occluded vessels leading to the infarcts were not observed, although many serial sections were studied. The nerve cells of the thalamus and those of the lenticular and caudate nuclei were normal. Blocks of tissue taken from the region anterior to the infarct were stained by the Marchi method. We were unable to observe any degenerated fibers which had arisen in the corpus Luysi passing orally or laterally into any of the nuclear masses at the base of the brain. Portions of the midbrain, the cerebellar peduncles, the pons and the medulla also were stained by the Marchi method. Degenerated myelin sheaths were observed to extend from the lesions in the subthalamic body to the medial lemniscus and then to pass down this bundle to its decussation (fig. 3). We are not certain as to their fate below this level; the blocks of tissue from the region of the dentate nuclei failed to be properly and completely impregnated with osmic acid. Some fibers which stained black with osmic acid extended toward the dentate nuclei. No fibers passed into the medulla, which was normal and was well impregnated with the osmic acid.

COMMENT

As has been pointed out by Martin, there is a definite syndrome of the corpus Luysi, which consists of violent hemichorea (hemiballismus) in which the movements have an unusual amplitude and force. The face or a limb on the affected side may be spared. If the face is involved, speech, swallowing and respiration are disturbed. The pyramidal tracts are not involved, and motor and sensory functions remain intact. Vegetative symptoms, such as changes in temperature and increased perspiration, and progressive mental changes ranging from excessive anxiety to delirium are frequently present but are neighborhood symptoms rather than specific symptoms. Death usually ensues in a few weeks and is attributable not to a cerebral or a cardiac cause but usually to complicating pneumonia.

As is demonstrated by our case and by some 25 cases reported in the literature, this syndrome is based on a destructive lesion involving the corpus Luysi. Since the recognition of the syndrome no case has been reported without a lesion involving the corpus Luysi. It is true that in several instances, as noted by Weil,[14] by Lloyd and Winkelman [13] and by Souques, Bertrand and others,[24] the pathologic process, besides involving the corpus Luysi, has affected the external nucleus of the thalamus, the anterior limb of the internal capsule and the corpus striatum. It is even possible that a lesion might be so situated as to disrupt the functions of efferent and afferent fibers of the corpus Luysi, thus producing hemichorea without direct damage to that body. No longer does a cerebral component in addition to pathologic change in the corpus Luysi appear necessary to the production of hemichorea. It appears to be true also that if the pathologic process is extensive and involves the pyramidal tracts, hemichorea does not develop, it being essential to the production of choreic movements that the neighboring structures be functionally intact. In our case at least half of

24. Souques, A., and Bertrand, I.: Sur la fonction motrice du corps strié à propos d'un cas d'hémichorée suivi d'autopsie, Rev. neurol. **33**:988-1002, 1926. Bertrand, I., and Garcin, R.: Étude anatomo-clinique d'un cas d'hemiballismus: Lésion dégénérative du corps de Luys et de la zona incerta, ibid. **2**:820-828 (Dec.) 1933.

the corpus Luysi was destroyed by an infarct. The only degenerated fibers that could be demonstrated were fibers extending from the corpus Luysi to the medial lemniscus and its decussation. We are not certain as to the fate of these fibers below this level. The fibers of Forel's bundle H_2 and the zona incerta were intact.

In spite of some evidence to the contrary, it appears that the term "hemiballismus" may be reserved for the syndrome of the corpus Luysi as considered in this discussion, the term "hemichorea" being left for the choreic disorders of movement occurring in childhood and in association with various conditions of which no comprehensive pathologic studies have been made. It is true that the movements in both conditions are of the same general pattern and result from pathologic changes affecting similar anatomic structures.

Hemiballismus usually occurs in elderly persons, although a few cases have been reported in which the patients were young. A vascular lesion is the most frequent cause, although metastatic carcinoma, tuberculosis, syphilis and metastatic abscess have been observed as etiologic factors. The onset is sudden; the course of the illness is progressive, death usually resulting within a few weeks or a few months. Rarely is there extension of the disorder to the opposite side, although several cases of paraballismus have been reported. In contradistinction, hemichorea is usually a disease of children or young adults and only rarely appears as a complicating factor in disorder of the brain of the adult. It is most frequently inflammatory, tending to be of insidious onset. Although it is progressive in its severity, it frequently involves the opposite side of the body. It usually tends toward recovery, although it may run a chronic course. Notwithstanding that the distinction between hemiballismus and hemichorea is not sharp, it seems that the term "hemiballismus" should be reserved for this clinicopathologic syndrome.

CONCLUSIONS

1. There is a specific syndrome resulting from damage to the corpus Luysi.

2. The syndrome probably is best designated by the term "hemiballismus."

Technical and Occasional Notes

PROGRESSIVE FALL IN PROTEIN CONTENT OF CEREBROSPINAL FLUID WITHDRAWN ABOVE A TUMOR OF THE CAUDA EQUINA

A Diagnostic Aid

HOWARD D. FABING, M.D., CINCINNATI

Cushing and Ayer [1] pointed out that the cerebrospinal fluid withdrawn from the region immediately above a tumor of the cauda equina is commonly xanthochromic and has a slight or marked increase in the protein content. This observation has been confirmed repeatedly and has come to be a valuable aid in the diagnosis of these neoplasms.

It occurred to me that as the cerebrospinal fluid is withdrawn from a point just cephalad to such a lesion it should, of necessity, become admixed with more normal fluid from higher levels and that its protein content should fall progressively as the fluid continues to flow. This assumption was submitted to chemical proof in the following case.

Mrs. F. H., aged 28, the wife of a farmer, began to experience shooting pain down the back of the right thigh in the spring of 1937. On occasion the pain radiated into the heel and on other occasions into the genitalia. In walking the patient experienced a sense of soreness in the right buttock. These symptoms increased in severity and were not relieved by uterine suspension and appendectomy in May 1937. Since the summer of 1937 she had been unable to ride in a car because of the aggravation of symptoms provoked by driving. Chiropractic treatments failed to relieve her, and she grew steadily worse.

In December 1937, in stooping to pick something from the floor, her right foot suddenly became weak, and she was unable to rise without help. After that she was forced to use a cane in walking, and there was some increase in the pain. Bladder symptoms were confined to occasional difficulty in starting the stream of urine. There was no alteration in libido sexualis. Defecation was normal.

The history by systems and the past and the family history were not contributory.

Neurologic examination disclosed that the cranial nerves and the upper extremities and trunk were normal. There were slight weakness of the flexor muscles of the thigh and profound weakness of the hamstring musculature bilaterally. There was profound weakness of the anterior tibial and the calf muscles bilaterally, with some atrophy of the right anterior tibial muscle. Movements of the toes were

---

From the Neurological Division of the Department of Internal Medicine, the University of Cincinnati College of Medicine.

1. Cushing, H., and Ayer, J. B.: Xanthochromia and Increased Protein in the Spinal Fluid Above Tumors of the Cauda Equina, Arch. Neurol. & Psychiat. **10**:167-193 (Aug.) 1923.

weak and limited. The knee and ankle jerks were absent bilaterally, and there was no plantar response. Sensory examination gave negative results except for an area of hyperalgesia in the second sacral dermatome on the right.

A diagnosis of tumor of the cauda equina, probably arising from the right second sacral root, was made.

Roentgenographic examination of the lumbosacral portion of the spine failed to reveal any lesion. A lumbar puncture needle was introduced in the second lumbar interspace. The fluid was released under 120 mm. pressure, and no dynamic block was demonstrated on jugular or abdominal compression. The fluid was released in amounts of 3 cc. in three consecutive test tubes. The fluid in the first tube was somewhat cloudy, and that in the second and third tubes was clear. The protein content of the fluid was: tube 1, 350 mg.; tube 2, 185 mg., and tube 3, 140 mg., per hundred cubic centimeters. The needle was then introduced in the fourth lumbar interspace, and a few drops of yellow fluid, which clotted quickly, was released; at this level there was complete dynamic block on jugular compression.

Exploratory laminectomy was performed by Dr. Frank Mayfield on Jan. 31, 1938. A cystic tumor extending from the level of the third lumbar vertebra to the tip of the sacral pouch was observed. The tumor was firmly attached to the right second sacral root. Microscopic study proved the tumor to be a perineural fibroblastoma, which had undergone cystic degeneration.

The patient made a prompt and uneventful recovery.

COMMENT AND SUMMARY

The protein content of the cerebrospinal fluid withdrawn from a point just above a tumor of the cauda equina is almost invariably high, whereas that of fluid withdrawn from higher levels is more normal. Therefore, as fluid is withdrawn progressively from a point immediately cephalad to such a tumor it should become diluted with more normal fluid from above, and its protein content should fall. A case is cited in which proof for this assumption was found.

The method of collecting a series of specimens of cerebrospinal fluid from a point just above a suspected tumor of the cauda equina and of examining each specimen for a progressive fall in protein content is offered, therefore, as an aid in the laboratory diagnosis of tumors of the cauda equina.

KETONEMIA IN CASES OF MENTAL DISORDERS

JOHN W. THOMPSON, M.B., CH.B.
AND
J. H. ASTE-SALAZAR, M.D.
Peruvian Fellow of the Rockefeller Foundation
BOSTON

In the course of experiments with "schizophrenic" patients designed to determine their response to the administration of epinephrine, some of the observations in the control series of experiments, in which epinephrine was not used, suggested deviation from the normal in the metabolism of carbohydrates and fats.

The patients were kept in a basal state and breathed through a mouth piece into a Tissot spirometer for three and one-half hours, i. e., for fourteen periods of fifteen minutes each. During each period a sample of expired air was taken, its oxygen and carbon dioxide contents were determined and the volume of ventilation recorded; during each period blood was drawn from the finger, and the dextrose and lactate contents were estimated; a sample of arterial blood was taken at the beginning, the middle and the conclusion of the experiment, and the oxygen and carbon dioxide contents and capacities were measured. The pulse and blood pressure were observed every five minutes throughout the experiment.

The first point of interest noted was that a drop occurred in the carbon dioxide curve for the third arterial sample as compared with that for the first. In 1 case, in the initial determination, the carbon dioxide combining capacity of the arterial blood, with the carbon dioxide tension at 40 mm. of mercury, dropped from 39.6 to 36.4 volumes per cent. The explanation was found in the urinalysis, which showed an output of acetone of 1.664 Gm. Since this ketosis was unexpected and was not found in any of the normal subjects who had been observed in the same way,[1] the possibility of its being a dietary phenomenon was controlled by giving the patients the same diet as the attendants at the hospital for eight days. It seemed unlikely that the phenomenon was the result of a simple dietary deficiency, since hospital patients live on a diet high in carbohydrates and low in fats and it was known that the weight of the patients studied had remained constant for a considerable period. The results obtained for the patients and the attendants further corroborated the difference, since none of the attendants showed significant ketonemia at the conclusion of the experiment, whereas the blood of the schizophrenic patients contained ketone bodies in amounts well above the upper limits of normal.

From the Fatigue Laboratory and the Department of Neuropathology, Harvard University, and the Metropolitan State Hospital, Waltham, Mass.

1. Dill, D. B.: Unpublished data.

Of what significance this observation may be in the pathologic picture of schizophrenia remains for future experimentation to decide, but we are of the opinion that in the cases which we studied there is a significant difference with respect to carbohydrate-fat metabolism in a fasting state from that of the normal subjects whom we have observed, as well as of those studied by Dill. A complete report is now being compiled and will appear shortly.

Dr. D. B. Dill collaborated with us in this work; Dr. Robert Johnson aided in the prosecution of the experiments, and Mr. Frank Consolazio and Mr. Douglas Fraser gave technical assistance.

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

At a meeting of the American Board of Psychiatry and Neurology held in New York on Dec. 29 and 30, 1938, the following diplomas were granted:

Without Examination.—Neurology and Psychiatry: Royall G. Cannaday, New York; Joseph Catton, San Francisco; David Corcoran, Central Islip, N. Y.; Gerald Orton Grain, Detroit; Ralph Nelson Greene, Coral Gables, Fla.; Roscoe W. Hall, Washington, D. C.; William H. Hengstler, St. Paul; Charles Henry Henninger, Pittsburgh; Edward Livington Hunt, New York; Raoul G. Provost, New Bedford, Mass.; Oscar Jacobus Raeder, Boston; Romney Ritchey, Alcatraz Island, Calif.; George Frederick Roeling, New Orleans; Samuel A. Silk, Washington, D. C.; Lewis Jeriah Smith, Brooklyn; Robert Wartenberg, San Francisco; Benjamin P. Weiss, Philadelphia; George Jesse Wright, Pittsburgh.

Psychiatry: Ira Maximillian Altshuler, Detroit; George K. Butterfield, Troy, N. Y.; Martin G. Carter, Los Angeles; James Arthur Cutting, Agnew, Calif.; Ruth Eldred Fairbank, Baltimore; Lucie Gabrielle Forrer, Palmer, Mass.; Thomas R. K. Gruber, Eloise, Mich.; Gilbert Hamilton, Santa Barbara, Calif.; W. J. Johnson, San Antonio, Texas; Lawrence K. Lunt, Concord, Mass.; Roy A. Morter, Kalamazoo, Mich.; Eugene W. Mullen, Agnew, Calif.; John P. H. Murphy, Washington, D. C.; Horace K. Richardson, Stockbridge, Mass.; Arthur Grant Rodgers, Central Islip, N. Y.; George H. Stevenson, London, Ontario, Canada; William Hastings Walker, Newton, Conn.

Neurology: Percival Bailey, Chicago; Albert Sturges Crawford, Detroit; Dorrell Ghio Dickerson, Los Angeles; *Gerald Reid Jameison, New York; *Douglas Armour Thom, Boston; *Erwin Wexberg, New Orleans.

With Examination.—Neurology and Psychiatry: Alexandra Adler, Boston; James L. Anderson, Miami, Fla.; Myer Asekoff, Danvers, Mass.; Benjamin H. Balser, New York; Abram Blau, New York; Louis Harold Cohen, Worcester, Mass.; Paul Dozier, Philadelphia; Hamblen C. Eaton, Harrisburg, Pa.; Joseph Epstein, Yonkers, N. Y.; Angus Macdonald Frantz, New York; Hugh M. Galbraith, Concord, N. H.; Riley Henry Guthrie, Boston; Robert R. Hays, Akron, Ohio; John A. Malcolm, Pittsburgh; Eli Marcovitz, Philadelphia; Eugene C. Milch, New York; Joseph Walker Owen, New York; Paul A. Petree, Harrisburg, Pa.; Kenneth G. Rew, New York; Philip Q. Roche, Philadelphia; Adolph L. Sahs, Iowa City; Samuel A. Sandler, Jersey City, N. J.; James Asa Shield, Richmond, Va.; Donald J. Simons, New York; Alexander Simon, Washington, D. C.; Joseph Stanley Skobba, Indianapolis; Winifred B. Stewart, Philadelphia; Hans Strauss, New York; Valentine Ujhely, Bath, N. Y.; John C. Urbaitis, Philadelphia; Foster L. Vibber, Worcester, Mass.

Psychiatry: Joseph L. Abrahamson, Brooklyn; Benjamin L. Allen, Wards Island, N. Y.; Camilla May Anderson, Philadelphia; Frances S. Arkin, New York; Francis J. Braceland, Philadelphia; Hollis E. Clow, White Plains, N. Y.; William Corwin, Waltham, Mass.; James M. Cunningham, Hartford, Conn.; Dorothy E. Donley, Boston; Calvin S. Drayer, Harrisburg, Pa.; Addison Duval, Washington, D. C.; Howard T. Fiedler, Westborough, Mass.; Harry Freeman, Worcester, Mass.; Jacob Henry Friedman, Bronx, N. Y.; William Gollick, Long Island, N. Y.; William F. Green, New York; Edgar Deucher Griffin, Washington,

D. C.; Edward O'Neil Harper, Cleveland; Herbert H. Herskovitz, Norristown, Pa.; Bartholomew Hogan, Washington, D. C.; William A. Hunter, East Gardner, Mass.; † Harold Kelman, New York; Elizabeth Kundert, Northampton, Mass.; Erich Liebert, Elgin, Ill.; Leo Maletz, Hathorne, Mass.; Hosea W. McAdoo, Arlington Heights, Mass.; Neil Thomas McDermott, Cleveland; Clementine C. McKeon, Waltham, Mass.; Nicholas Michael, Columbus, Ohio; † Clarence Wilmott Olsen, Los Angeles; Grosvenor Pearson, Foxborough, Mass.; Manson B. Pettit, Washington, D. C.; Robert J. Phifer, Wernersville, Pa.; † Raul Pietri, Asbury Park, N. J.; Edward F. Reeser, Huntington, W. Va.; Evelyn B. Reichenbach, Washington, D. C.; † John H. Scharf, New York; Doris M. Sidwell, Hathorne, Mass.; Anthony S. Tornay, Philadelphia; Edgar Trautmann, New York; Exie E. Welch, Indianapolis; Paul H. Wilcox, East Gardner, Mass.; Bruno E. Zawacki, Northampton, Mass.

Neurology: *Irma Bache, Boston; Bernard S. Brody, New Haven, Conn.; *Lewis Doshay, Bronx, N. Y.; *Jacob Goldwyn, Worcester, Mass.; Yale David Koskoff, Pittsburgh; H. Russell Meyers, Brooklyn; G. Wilse Robinson Jr., Kansas City, Mo.; *Philip Solomon, Brookline, Mass.; Melvin W. Thorner, Philadelphia; Richard Wilson, Atlanta, Ga.

* This award is supplementary to one previously granted in psychiatry.

† This award is complementary to one previously granted in neurology.

CORRECTIONS

In the article by Dr. Clemens E. Benda, "Studies in Mongolism: I. Growth and Physical Development," in the January issue (ARCH. NEUROL. & PSYCHIAT. **41**:83, 1939), the word "first" in the second line on page 94 should read "last," and the word "latter" in the sixth line on the same page should read "former."

In the article by Drs. Arthur D. Hirschfelder and Victor G. Haury entitled "Variations in Magnesium and Potassium Associated with Essential Epilepsy," in the July issue (ARCH. NEUROL. & PSYCHIAT. **40**:66, 1938), the word "unfiltrable" in the third line of the paragraph bearing the side heading "Normal Persons" on page 78 should read "ultrafiltrable."

Abstracts from Current Literature

Physiology and Biochemistry

A Physiological and Histological Study of the Frontal Cortex of the Seal (Phoca Vitulina). David M. Rioch, Biol. Bull. **73**:591 (Dec.) 1937.

The "motor areas" of the cortex of the cat, dog and bear have been investigated recently with the combined methods of electrical stimulation and histologic examination. It was of interest, therefore, to make a comparative study of the harbor seal. The exposed cortex of the frontal lobe of the left hemisphere of 6 young seals (Phoca vitulina), when under dial anesthesia, was stimulated electrically. Movements of the tail, both hindflippers, the contralateral foreflipper, neck and face were evoked. Histologic examination of the frontal lobe of 3 animals revealed a well developed cortex divisible into cytoarchitectural areas structurally similar to those in other carnivores, but differing in their extent and relation to the sulci. On the basis of comparison of the seal and the terrestrial carnivores, Rioch concludes that the degree of differentiation of the cortical representation should be correlated with function and not with form.

Cobb, Boston.

Limits of Variation of the Synaptic Delay of Motoneurons. Rafael Lorente de Nó, J. Neurophysiol. **1**:187 (May) 1938.

The average synaptic delay of ocular motoneurons measures 0.7 millisecond. It may be shortened by facilitation or by increasing the number of activated synapses, and it may be lengthened by decreasing the stimulus or by raising the threshold of the motoneurons. The minimal synaptic delay measures from 0.5 to 0.6 millisecond, and the maximal delay, from 0.8 to 0.9 millisecond. The minimal synaptic delay is equal to the duration of the major part of the spike potential at the synaptic knobs. Lorente de Nó states that knowledge of the temporal course of synaptic transmission is not sufficient to identify the elementary process underlying transmission, but reduces the number of possible assumptions. No process may be assumed that cannot take place within the now known rigid time constants.

Alpers, Philadelphia.

Synaptic Stimulation of Motoneurons as a Local Process. Rafael Lorente de Nó, J. Neurophysiol. **1**:195 (May) 1938.

Lorente de Nó finds that although the threshold stimulation of motoneurons requires that several impulses be delivered simultaneously at their synapses, not all the fibers contributing to the synaptic scale need be active. Experimental results demonstrate that while the activation of a large number of synapses may remain ineffective, activation of a limited number of the synapses, effected simultaneously with the stimulation of other fibers, results in the setting up of a response. Furthermore, he finds that effective stimulation of motoneurons may be produced by activation of various groups of fibers. Anatomic studies have revealed that the synaptic scale of the motoneurons consists of interlacing clusters of knobs belonging to a larger number of fibers and that the synaptic terminals of each fiber are located at some distance from one another. Activation of all the synaptic knobs at any discrete zone of the soma demands that several fibers be conducting impulses. It is obvious that different groups of fibers will cause stimulation at different zones of the soma.

Lorente de Nó concludes, therefore, that the setting up of a new impulse by the motoneuron results from a localized process taking place underneath a dense

group of active synaptic knobs. Subliminal responses must be propagated decrementally, but the information available is insufficient to estimate the amount and rate of the spread.

ALPERS, Philadelphia.

ANALYSIS OF THE ACTIVITY OF THE CHAINS OF INTERNUNCIAL NEURONS. RAFAEL LORENTE DE NÓ, J. Neurophysiol. **1**:207 (May) 1938.

The nervous system is composed of an exceedingly large number of interlacing pathways which offer numerous opportunities for the conduction of impulses along divergent paths, but during activity it becomes fractionated into a group of active and a group of inactive neurons. The active neurons are arranged in convergent chains of relatively simple composition, which may be called the multiple and the closed chain, through which impulses circulate. The fractionation is attributable to the fact that stimulation of a neuron requires the activation within a short period, which for the motoneurons is less than 0.3 millisecond, of several synapses having a determined spatial distribution on the neuron. The rigidity of the conditions necessary for the effective summation of impulses delivered to synaptic junctions is such that the impulses circulating through the active chains, despite their being numerous, remain subliminal for neurons of the inactive group.

Impulses circulating through the chains of neurons of the internuncial system create a statistically constant stimulus of motor and internuncial neurons, as both classes of neurons are submitted to constant bombardment by delivery of impulses at their synapses. The neurons respond rhythmically at a rate dependent on the strength of the bombardment and the rate of their recovery.

The multiple chain of neurons is the elementary unit of transmission; it supersedes the classic reflex arc with a fixed number of synapses. The rate at which a multiple chain may transmit impulses depends on the number of neurons it contains; the greater the number of links the lower the minimal rate.

The closed chain of neurons may play different roles, according to the number of links that it contains. If the number is small activation of the chain may result in inhibition, but if the number of links is large enough it may result in sustained facilitation or discharge. It is indicated that after-discharge does not necessarily require autochthonous activity of closed chains of neurons; after-discharge must be interpreted rather as a special case of reflex reversal, maintained by closed chains of neurons which keep the constant stream of impulses arriving from the periphery or from other centers within channels opened by the intercurrent stimulation.

ALPERS, Philadelphia.

SOME REMARKS ON THE PHYSIOLOGY OF THE CEREBRAL CIRCULATION. F. L. GOLLA, J. Ment. Sc. **83**:505 (Sept.) 1937.

Brain cells have a greater need for oxygen than other tissues of the body. The brain in man represents 2 per cent of the body weight, but it utilizes 10 per cent of the total oxygen consumed by the body. The gray matter in the cortex consumes ten times as much oxygen as the white matter. The brain cannot establish an oxygen debit; it must be constantly supplied with oxygen by the circulating blood. The amount of blood flowing through the brain is difficult to determine, but a conservative estimate shows that 100 Gm. of brain receives 40 Gm. of blood per minute. Irrespective of what happens to the body, the brain always receives its quota of blood. It is an interesting question whether additional activity of any portion of the brain is accompanied by increased blood flow to that portion. It is known that various stimuli increase the temperature of the brain. Oxygen consumption is also increased. Thus, in experimental convulsions induced by strychnine the animal uses 700 per cent more oxygen than the resting animal. The chief site of metabolism is in the synapse. A detailed study of the nerve supply to the blood vessels of the brain shows that they are amply supplied by vasodilator nerves. No one as yet has demonstrated vasoconstrictor sympathetic

fibers to the vessels of the brain. Stimulation of the cervical portion of the sympathetic chain has no effect on the cortex or the vessels of the brain. Golla speculates on the reasons for the absence of the vasoconstrictor fibers and concludes that the impulses are conveyed chemically rather than by means of fibers.

KASANIN, Chicago.

THE ELECTROENCEPHALOGRAM IN CERTAIN PATHOLOGIC CONDITIONS. G. MARINESCO, O. SAGER and A. KREINDLER, Presse méd. **46**:650 (April 27) 1938.

Marinesco and his associates made electroencephalograms either with the method of Berger, by attaching the needles to the anesthetized scalp, or by applying impolarizable electrodes to the shaved scalp. They regard the frequency of the alpha waves as the most constant characteristic of an electroencephalogram; in the same subject these waves maintain the same level during the duration of the recording. The authors regard as anomalies considerable diminutions and augmentations of the frequency which occur transiently in the course of the recording. On the other hand, the amplitude of the waves varies considerably in the course of a recording. In certain pathologic conditions several modifications may become manifest. In this paper the authors report their observations on the electroencephalograms of patients with such disorders as tetany, epilepsy, aphasia, cerebral tumor and coma. They found that in some pathologic conditions the anomalies of the electroencephalogram consisted especially of modifications of amplitude (epilepsy, tetany) or of amplitude and frequency (aphasia, cerebral tumors). Cases of disease in which there are modifications of frequency but not of amplitude are extremely rare. Generally, diminution in frequency is accompanied by diminution in amplitude, as in cases of aphasia and certain cerebral tumors, and even by augmentation of amplitude, as in a case of coma. Nevertheless, there are exceptions. In some cases of aphasia reported, the frequency alone was diminished. This reduction in frequency was accompanied, if not by modification of amplitude, by intercalation of long pauses. In 2 cases of cerebral tumor the authors encountered augmentation of frequency (15 hertzian waves in 1 and 18 hertzian waves in the other) without modification of amplitude. Likewise, in cases of dementia paralytica the authors occasionally encountered diminution in frequency without modification of amplitude. In the 90 cases of pathologic states studied, the authors observed this only eight times.

EDITOR'S ABSTRACT.

ALCOHOLIC SLEEP. I. BOBKOV and N. ASTAPOV, Arkh. biol. naouk **45**:59, 1937.

Bobkov and Astapov studied the various factors which influence the action of alcohol in rabbits, dogs and cats. With the animal under ether narcosis they drained the cerebrospinal fluid through a suboccipital puncture; from twenty-five to thirty minutes later the animal was given pure alcohol by gavage. Animals serving as controls were given the same amount of alcohol. About from seven to ten minutes later the animals the spinal fluid of which had been drained became intoxicated and passed into a state of narcosis which lasted from four to seven hours. While the animals used as controls also became intoxicated, their intoxication was milder, and narcosis failed to develop. The authors conclude that the difference in the action of the alcohol in the two groups of animals was due to a change in meningeal permeability caused by removal of the cerebrospinal fluid. They concluded that in the animals subjected to drainage a greater amount of alcohol reached the brain. They theorized further that the drainage produced changes in hydrogen ion concentration (p_H), and since the p_H of the brain was higher than that of the blood, elimination of the cerebrospinal fluid probably lowered the hydrogen ion concentration of the brain. This biochemical change allowed better penetration of the alcohol into the brain.

NOTKIN, Poughkeepsie, N. Y.

Neuropathology

SYMMETRIC HEMORRHAGIC NECROSIS OF THE CEREBRUM FOLLOWING PRIMARY THROMBOSIS OF THE SUPERIOR LONGITUDINAL SINUS. EDWIN F. HIRSCH, Arch. Path. **26**:210 (July) 1938.

Hirsch reports a case of symmetric cerebral necrosis following thrombus of the superior longitudinal sinus. The disease occurred in a woman aged 54 two days after a fall. Severe headache with unconsciousness occurred for twenty-four hours. There was no paralysis or incontinence. Physical examination showed absence of abdominal reflexes and choked disks. A clinical diagnosis of hemorrhagic encephalitis was made.

Gross examination of the brain showed thrombosis of the superior longitudinal sinus with symmetric hemorrhagic areas, 5 cm. in diameter, in the motor areas 2 cm. from the median line. The symmetry of the lesions was explained by the extension of the thrombosis into cerebral veins on each side of the median line.

WINKELMAN, Philadelphia.

MYELOMA AND ITS NEURAL COMPLICATIONS. CHARLES DAVISON and BEN H. BALSER, Arch. Surg. **35**:913 (Nov.) 1937.

Twelve cases of multiple myeloma are reported. In 6 in which autopsy was performed, involvement of the spinal cord, spinal nerve roots, peripheral nerves or brain was observed. In 6 cases in which there were signs of lesions of the spinal cord or roots, the neural structures were not removed. In most of the cases of lesions of the spinal cord the neurologic symptoms were produced by compression of the vessels of the cord. A myelopathic process resulted from interference with the circulation. The damage to the fiber tracts depended on the degree and duration of the compression. In case 1 there was direct metastasis to the spinal dura. Herpes zoster, noted in a number of the cases, was caused by direct compression of the spinal roots by the neoplasm. In 1 case peripheral neuritis was probably due to compression of the brachial plexus, severe anemia or unknown toxic factors. In another case the myelomatous nodules of the cerebral dura and skull resulted in interference with the cerebral circulation and production of paranoid psychosis.

GRANT, Philadelphia.

DEGENERATION OF THE GLOBUS PALLIDUS AFTER NITROUS OXIDE ANESTHESIA. C. NORMAN ABBOTT and CYRIL B. COURVILLE, Bull. Los Angeles Neurol. Soc. **3**:46 (March) 1938.

The neuropathologic changes observed in patients who died only a few days after anesthesia induced with nitrogen monoxide are limited to small groups of cells in the cortex and lenticular nucleus and are easily overlooked on cursory examination. With longer periods of survival the lesions are more marked and occur with great regularity in the form of necroses, especially in the globus pallidus. The clinical manifestations of such changes resemble those of progressive lenticular degeneration or parkinsonism, with associated psychic symptoms. Abbott and Courville report the case of a woman aged 37 on whom cholecystectomy was performed under general anesthesia induced with nitrogen monoxide, oxygen and ether, and maintained by a mixture of ethylene, oxygen and ether. When the anesthetic was changed there was marked cyanosis, which persisted for several minutes, and respirations were irregular during the rest of the operation. The patient remained comatose for two days, then gradually improved. There was marked retardation of speech. On the twenty-fifth day after operation frontal headaches, haziness of vision and faintness appeared, and the patient became mentally confused, disoriented and incontinent. The spinal fluid was normal. On the forty-second day after operation she again lapsed into coma and died a few hours later. Autopsy revealed partial necrosis of the globus pallidus bilaterally. Microscopically, the central

portion of the necrotic areas was surrounded by a zone of degeneration and gliosis, with phagocytes laden with degenerating myelin. Ganglion cells in numerous other portions of the brain showed fatty degeneration, but no definite foci of necrosis were seen in the cortex. The arachnoid was slightly thickened, and the oligodendroglia cells of the white matter were acutely swollen and proliferated. Abbott and Courville attribute the lesions to cerebral asphyxia and absolve the ethylene of primary blame. The similarity to carbon monoxide poisoning is notable.

MACKAY, Chicago.

MENINGO-ENCEPHALO-MYELORADICULITIS. P. GOOLKER, J. Nerv. & Ment. Dis. **87**:405 (April) 1938.

Goolker records the case of a woman aged 53 who since early childhood had had frequent inflammation of the eyes and four operations for relief from maxillary sinusitis. Disturbance of many cranial nerves on the left side gradually developed. There were pallor and edema of the optic disk, dilatation and immobility of the pupil, anesthesia of the area of distribution of the ophthalmic division of the trigeminal nerve and peripheral paralysis of the left facial nerve, with loss of taste in the anterior two thirds of the tongue. There were some inequalities in the reflexes and an equivocal Babinski reaction on the left side. The temperature varied from 99 to 101 F. The spinal fluid contained 57 cells per cubic millimeter, predominantly lymphocytes, and 87 mg. of total protein per hundred cubic centimeters. Pneumonia developed, and the patient died after eight days, the clinical diagnosis being bronchopneumonia and encephalomyelitis with involvement of peripheral nerves.

The neuropathologic observations included subacute inflammation of the pia-arachnoid, most marked about the brain stem and spinal cord but present over the cerebral cortex, with edema, thickening and infiltration with lymphocytes and plasma cells. The cranial and spinal nerve roots were encased in the inflammatory exudate. There were occasional areas of rarefaction in the cerebral cortex and subcortex. Perivascular infiltration with lymphocytes and compound granular cells was seen in the cerebrum and brain stem. Mild, diffuse destruction of myelin was seen in the peripheral fiber tracts of the brain stem, while in the spinal cord extensive areas of destruction of myelin occurred, particularly in the dorsal columns. These areas were more or less circumscribed, but there was also diffuse dissolution of myelin in the periphery of the lateral and anterior columns. The myelin sheaths were swollen, vasculated, broken down into globules or entirely dissolved. Fat globules of varying size were observed. The axis-cylinders were better preserved than the myelin. The ganglion cells of the spinal cord appeared large and in some sections contained fat. The oligodendroglia cells were somewhat increased. The peripheral nerves also showed destruction of myelin and formation of fat.

Goolker characterizes these changes as both inflammatory and degenerative and places them in the group of "acute disseminated demyelinating encephalomyelitis," except that the meningeal involvement was greater than is usual in such cases. The demyelinated areas bore no relationship to the blood vessels and were most numerous and severe in the spinal cord. The etiologic agent must remain undetermined; it was probably infectious and connected with the maxillary sinusitis.

MACKAY, Chicago.

CLINICAL AND ANATOMIC STUDY OF LATE CEREBELLAR ATROPHY WITH CORTICAL PREDOMINANCE. A. DE HAENE, J. belge de neurol. et de psychiat. **37**:427 (July) 1937.

De Haene reports a case of delayed cerebellar atrophy occurring in a man aged 60. Pathologically, the condition was characterized by degeneration of the Purkinje cells, the ascending fibers and certain areas of the cerebellar cortex.

There was secondary degeneration in the olivary bodies. The changes were symmetric, and the ventral spinocerebellar tracts and the nuclei of Goll and Burdach were intact. The cortex, thalamus, basal ganglia and spinal cord showed no changes except hypoplasia of the nucleus of the left oculomotor nerve. There had been congenital paralysis of this nerve. The author believes that alcohol should be considered as a possible etiologic factor in cases of atrophy of the cerebellar cortex.

DE JONG, Ann Arbor, Mich.

CHIASMAL CHANGES ACCOMPANYING ARACHNOIDITIS OF THE OPTIC CHIASM. M. BELADO and E. FRANKE, Arch. argent. de neurol. **16**:119, 1937.

Belado and Franke report the case of a patient who had bitemporal hemianopia, most marked in the external isopters, and severe disturbance in the right macular field. There was paralysis of the left sixth nerve. The right optic disk was pale. Ventriculographic examination with iodized poppyseed oil showed small lateral ventricles, the third ventricle not being visualized. A diagnosis of arachnoiditis of the chiasm was made. Operation revealed thickening of the arachnoid, which was adherent to the chiasm and to the right optic nerve. The arachnoid was removed. The patient died thirty-six hours after the operation. Necropsy showed a greatly thickened arachnoid at the base of the brain, especially in the area around the chiasm and right optic nerve. Microscopic study showed infiltration of the chiasm and optic nerve at the point of insertion of the arachnoid. The infiltration was composed of lymphocytes and plasma cells; it followed the interfascicular septums passing from the arachnoid into the nerve. It was limited to the periphery of the nerve and was present at all points in contact with the arachnoid. There was destruction of both the myelin sheaths and the axis-cylinders in the areas involved, and these areas contained abundant compound granular corpuscles. This indicates that the process was inflammatory and resulted from an acquired infection.

NORCROSS, Philadelphia.

ALTERATION OF BENIGN GLIOMAS (ASTROCYTOMAS) TO MALIGNANT GLIOBLASTOMAS. J. SCHEINKER, Deutsche Ztschr. f. Nervenh. **145**:45, 1938.

Scheinker reports 3 cases of gliomas in which no radical operation was performed. The tumors showed marked changes of tissue structure after the first operation, as determined by specimens taken at subsequent operations and at autopsy. At the first examination the specimen in each case proved to be a typical astrocytoma, which later changed to a malignant undifferentiated glioblastoma multiforme. It is suggestive that a close histogenetic connection exists between astrocytoma and glioblastoma. This observation suggests the possibility of change of a benign astrocytoma to a malignant tumor.

ADLER, Boston.

SITE AND NATURE OF DISEASE IN THE LIGHT OF TOPISTIC INVESTIGATION OF THE BRAIN. C. VOGT and O. VOGT, J. f. Psychol. u. Neurol. **47**:237 (April) 1937.

This contribution is a continuation of researches begun in 1921 on what the Vogts designated as *Pathoklise*. In their first publication, they presented evidence that both the gray and the white matter of the brain can be divided into topistic units which, owing to their anatomic peculiarities, have characteristic biologic manifestations. The anatomic peculiarities of any given unit can be seen not only in its nerve cells but also in its glia and its vascular supply. The question arose as to how far these peculiarities in a topistic unit affect the specific biologic manifestations; this article is the authors' answer to this question.

From a cytoarchitectonic, myeloarchitectonic and angiotectonic investigation of the brain in various diseases, the Vogts established a definite topistic character for premorbid changes and a probable one for certain predispositions to disease. At the same time, they observed that the particular structure of an affected topistic

unit is the only cause for the topistic localization of the alterations due to disease. They found that the topistic unit is the carrier of specific functions and, in disease, of the pathologic formative processes, so that in all topistic diseases the same disease factor always produces similar symptoms. With this concept in mind, the observation of structural changes in altered topistic units may lead to an understanding of individual, as well as of familial, deviations.

According to the authors, many focal diseases of the brain have a topistic character. This applies not only to hereditary but to toxic, infectious and vascular diseases. Primary topistic organic disease of the vessels is rare. The occurrence of such functional changes in the caliber of the vessels has thus far not been established. On the other hand, atopistic variations in the caliber of the blood vessels produce topistic diseases in the same manner as other atopistically distributed noxae. A specific structure reacts to definite causes with definite disease processes.

The authors emphasize that they did not limit the concept of *Pathoklise* (disposition to disease dependent on structure) to nerve parenchyma. They believe that in final analysis physicochemical peculiarities are determinants of *Pathoklise*. They base this belief on their determination of the functional peculiarities of architectonic units, which has been fully confirmed by Spielmeyer.

Depending on the intensity and nature of the disease process, the Vogts divide *Pathoklise* into several subgroups. Thus, area h shows increased severity of involvement, as compared with the other regions of the cornu ammonis. The putamen and other nuclei are more often diseased than the rarely affected nucleus ruber; this the authors designate as general Klise. A topistic unit may react to different causes with a similar, or almost similar, process; an example of this is hypermyelination, which may be caused by traumatic, vascular or infectious factors; this is designated as specific Klise. The tendency for a definite disease factor to react with a single process is designated as special Klise. Not infrequently, a special *Klise* may develop into a specific *Klise*.

The authors believe that the entire concept of *Pathoklise* may apply not only to disease of the mind and nervous system but to disease of any organ. They believe also that a better understanding of the determinants of the site of disease and of the physicochemical effects of the constitution of the respective topistic units may pave the way to rational therapy.

KESCHNER, New York.

WILSON'S DISEASE IN TWO SIBLINGS. HEINRICH SCHWYN, Schweiz. Arch. f. Neurol. u. Psychiat. **40**:221, 1937.

Schwyn states that Wilson's disease occurs most frequently in large families and that a single case in one family is rarely encountered. Although the age at onset usually falls between the seventh and the fifteenth year, the malady has been known to appear as late as the fourth decade. The course is generally more rapid in younger patients. The 2 patients whose histories are reported had 14 brothers and sisters, 3 of whom died in infancy. The oldest sister and a maternal aunt were patients in hospitals for mental disease; a maternal uncle had epilepsy. The father, though a good worker, was quiet and peculiar. Both patients made good progress in school and had subsequently been industrious. The first, a woman aged 22, presented as initial symptoms marked fatigability, stubborn insomnia, inappetence and unsteadiness of gait. After about three weeks, loss of facial expression and stooped posture were noted. The prevailing mood from the beginning was one of depression; the patient became apathetic, expressed ideas of poverty and made two suicidal attempts. On examination, ten months after the onset, seborrhea of the face, stiffness in mimetic movements, with the features set in a fixed smile, and psychomotor retardation were observed. Speech was slow and monotonous; chewing and swallowing were difficult; movements of the extremities were slow and awkward, and there was a fine tremor of the hands. The patient was unable to care for herself and had incontinence of urine. About fourteen months after the

onset, she became acutely ill with fever and abdominal pain and died in a few days. Autopsy revealed, in addition to serofibrinous peritonitis, a grossly nodular liver, chronic swelling of the spleen and punctate hemorrhages in the region of the basal nuclei. The hemorrhages were most numerous in the corpus striatum, which presented other grossly visible changes. Microscopic examination of the tissues is not reported.

The second patient, a younger brother of the first, on entering military service in his nineteenth year seemed tired and lacking in energy. He had a seizure, which was thought to be hysterical, and it was subsequently learned that he had become depressed and apathetic several months before this attack. On return from service two months later, changes in character were evident; he was restless, excitable, given to silly jokes, sexually aggressive and alternately depressed and elated. During a period of vagrancy several months later, he fell frequently, finally injuring himself; on return home his face was masklike, and he showed little interest in his surroundings. In spite of the increasing physical and mental disability, however, he found employment and later served the required two weeks with the militia. When examined nearly two years after the onset, his face was greasy and expressionless, speech slow and monotonous and the posture stooped. The muscles of the extremities were rigid, and there was a fine tremor of the hands. Examination of the corneas with a slit lamp disclosed a pigmented ring in Descemet's membrane. No defect of intelligence was revealed by formal tests, but the patient was depressed and tearful; there was general slowing of the mental processes, and the behavior was characterized by childish indifference. A mixture of scopolamine and atropine afforded no symptomatic relief. The patient died, apparently of septicemia complicating cellulitis of the forearm two and one-half years after the onset. A firm, finely nodular liver and chronic swelling of the spleen were observed at autopsy. There were slight atrophy of the frontal lobes and more marked atrophy of the putamen of both sides. Microscopically, there was extensive destruction of both small and large ganglion cells in the putamen, with glial proliferation, deposits of fat in gitter cells and lying free in the tissues and a marked increase in iron content. The numerous blood vessels, mainly precapillaries, in the caudal portion of this structure were surrounded by scavenger cells and in places by lymphocytes and polymorphonuclear leukocytes. Large glia cells of Alzheimer type I and clumps of somewhat smaller cells, corresponding to Alzheimer type II, were seen in the putamen. Similar, but less pronounced, glial changes, with occasional perivascular infiltrations, were seen in the caudate nucleus, the corpus Luysi and the substantia nigra. The cerebral cortex, particularly the third and fifth layers, showed glial alteration and a few cells of Alzheimer type II. Changes in ganglion cells with moderate proliferation of glia were noted in the dentate nucleus and in Bergmann's layer of the cerebellar cortex.

Schwyn expresses the view that in the cases reported here it is possible that a tendency to mental disturbance was inherited with the recessive anlage for Wilson's disease and that the latter condition merely served to precipitate the psychosis.

DANIELS, Denver.

DEATH DURING THE COURSE OF INSULIN THERAPY IN A CASE OF SCHIZOPHRENIA. RUDOLPH LEPPIEN and GERD PETERS, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:444 (Nov.) 1937.

Leppien and Peters report the case of a boy aged 18 years who died during insulin therapy. Autopsy showed congestion of the pial vessels. There was a small subpial hemorrhage over the left cerebellar hemisphere. The intracerebral vessels all seemed congested. There were a few perivascular hemorrhages in various parts of the brain, without any surrounding glial reaction. In the white substance of the brain, especially in the occipital region, there were small collections of glia cells, some of them perivascular. Similar glial changes were seen in the nuclei of the medulla. There were diffuse changes in the ganglion cells in all parts of the cortex, especially in the central region. The cells were swollen and vacuo-

lated; the tigroid substance was unstained, and the cells were pale and homogeneous. The large cells of the corpus striatum and the cells in the olivary and dentate nuclei showed similar changes. There was compensatory gliosis in the affected parts of the brain. Ischemic changes in groups of ganglion cells were noted in lamina III. A small fresh area of softening was present in the cornu ammonis. A few of the cerebral vessels showed swelling of the endothelial lining. The myelin sheaths and axis-cylinders were intact. Most of the changes in the brain were due to the effect of the insulin on the cerebral circulation. Vasospasms probably accounted for many of the changes. A direct toxic effect of the insulin on the ganglion cells was also probable, considering the nature of the cellular changes.

SAVITSKY, New York.

SENILE CHANGES IN THE BRAIN IN DEMENTIA PARALYTICA. SIN-ITI SEKINE, Psychiat. et neurol. japon. **42**:18 (March) 1938.

Sekine reports the case of a man aged 58 with dementia paralytica, who was treated with malaria and died after eleven years. In silver preparations the frontal cortex presented changes in the ganglion cells affecting the neurofibrils, similar to those seen in senile disease. There were also changes resembling senile plaques.

ALPERS, Philadelphia.

INVOLUTIONAL PSYCHOSIS WITH PSEUDOSCLEROTIC CHANGES IN THE BRAIN: REPORT OF A CASE. MITIO WATANABE and SABURO OKUDA, Psychiat. et neurol. japon. **42**:18 (March) 1938.

Watanabe and Okuda report the observations in the central nervous system of a woman aged 55 with involutional psychosis, who died of acute uremia a year and a half after the development of the psychosis. Throughout the cerebral cortex and basal ganglia were large, atypical glia cells of the Alzheimer type. There was present also circumscribed status spongiosus in the motor cortex and in the dorsolateral portion of the putamen on both sides. In addition, the brain showed a small area of softening in the region of the aqueduct of Sylvius, a smaller incomplete area of necrosis in the caudate nucleus and a few glial rosettes in the pallidum. The brain showed no arteriosclerotic changes. The changes in the brain resembled closely those in pseudosclerosis.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

RELATION OF INCREASED VITAMIN B (B_1) INTAKE TO MENTAL AND PHYSICAL GROWTH OF INFANTS. M. G. COLBY, I. G. MACY, M. W. POOLE, B. M. HAMIL and T. B. COOLEY, Am. J. Dis. Child. **54**:750 (Oct.) 1937.

Twenty-five normal infants were given a diet containing from 2 to 2.7 Sherman-Chase units of vitamin B per gram of solids during the first year of life and were compared with two groups of infants of the same number and age, serving as controls, who were given an identical diet except that it contained from 0.7 to 1 unit of vitamin B per gram of solids. After six months the ratio was changed to 320 units daily for the experimental group and 227 units for the control groups.

Physical examination, including seventeen anthropometric measurements, hemoglobin estimation, a red blood cell count and roentgenographic examination of the long bones and measurement by the planimeter, was made every month. The conclusion was reached that increased amounts of vitamin B_1 seem "to promote a more stabilized growth and greater nutritional stability."

Observations of sixty-five behavior items, including the Gesell and Bühler-Hetzer normative tests, deep and superficial reflexes and additional discrimination and learning tests, were measured at the 6, 9 and 12 month levels. At the

6 month period the definite superiority of the experimental group was shown by increased speed of responses, specificity of reaction and accelerated coordination of the anterior postural reflexes; the changes were characterized qualitatively as indicative of early maturation of behavior patterns, increased alertness in attention and perception and acceleration of learning. The difference between the groups was much less marked at the 9 month period and was minimal at the 12 month level.

WAGGONER, Ann Arbor, Mich.

PSYCHOSIS AND THE CENTRAL AUTONOMIC NERVOUS SYSTEM. H. D. SINGER, J. A. M. A. **110**:2048 (June 18) 1938.

Singer proposes to present considerations for a reorientation of the point of view, not with the object at present of propounding a new system of classification, for which there is yet insufficient knowledge, but as a guide to the analysis of clinical material and the prosecution of research. It will probably be conceded without question that what underlies mental illness is some disturbance, due either to a structural lesion or to situational stress, in the central integrating mechanisms of the organism. The term psychosis may be used profitably to designate active disorder in behavior resulting from structural damage of the central machinery of autonomic integration, specifically dynamic or "energy" disorders. The term psychoneurosis may, in contrast, be used to designate maladjustments (psychogenic) to situations in life, and when employed in this sense will include examples of what today are grouped as psychoses; the behavior constituting a psychoneurotic adjustment may require commitment of the patient. Examples of structural damage or defect, either congenital or acquired, of the central autonomic nervous system include schizophrenic dementia simplex, psychopathic personality, some forms of "neurasthenia," the "organic" psychoses, involutional melancholia, many manifestations of chronic encephalitis and affective changes following frontal lobectomy. In addition, there belong in this group many of the so-called functional psychoses, whether manic-depressive, schizophrenic or paranoid in form, even though the nature of the lesion is unknown. There is an essential difference between the symptoms produced by the illness, which includes the fact of psychosis, and those which express the form of the psychosis. The former are determined by the nature and location of the structural damage, and the latter, by the personality of the person who is ill. Thus, one and the same organic lesion, even though its nature may be unknown, may give rise to a manic-depressive form of psychosis in one person and to a schizophrenic or paranoid psychosis in another. The use of the form of psychosis as a basis of correlation with observed physiologic disturbances will yield little of value as regards the pathologic condition concerned in giving rise to the fact of psychosis. The form of the psychosis is of paramount value in the study of personality.

EDITOR'S ABSTRACT.

LANGUAGE STUDY IN SCHIZOPHRENIA. WILLIAM L. WOODS, J. Nerv. & Ment. Dis. **87**:290 (March) 1938.

Woods studied verbatim reports of conversations with 125 psychotic patients, with especial attention to disturbances of language and thought in schizophrenia. The thought of the schizophrenic person seems to be composed of diffuse affect rather than of precise ideation. Vague emotional states and subjective phenomena are expressed in superficially conventional language, which lacks simplicity and directness because of its nebulous content. There is often a preference for abstract words in a florid style which hides a lack of precision in meaning. In contrast to this inexact, verbose structure, other patients tend toward a more circumscribed and condensed speech. The use of indefinite pronouns leaves the listener unoriented; the subject of the sentence is omitted; all unnecessary parts are excluded from speech, and the action of the idea alone remains. The proverb "early bird catches the worm" becomes "first up," and "barking dogs never bite," simply "bluff."

Other condensations consist of the use of single words or phrases as fixed symbols of complex ideas, such as the word "northwestern" to mean privation, sturdiness and struggle, as depicted in a moving picture about Alaska. This form of condensation, present in normal persons, becomes pathologic when the patient uses it with a purely egocentric significance and without any effort to render it meaningful to the listener. Similarly, neologisms, impromptu or repeated and stereotyped, are invented to signify the inner personal ideas of the patient without any effort at translation into conventional speech. Metaphor, so frequently employed by schizophrenic persons, is again used with purely egocentric connotations and without regard to conventional understanding. The metaphor is therefore bizarre and eccentric.

The unit of thought in more deteriorated schizophrenic patients is not the idea contained in a well organized sentence but that expressed in a word. Woods applies the term "category" to this unit. The deteriorated schizophrenic patients deal with this smaller unit because they cannot grasp more complicated material. The broad conceptual idea underlying a complete sentence is too complex for them. Since one category may belong to many systems, these associations may lead off in a new direction at any time. Categories tend to be unstable and unprecise and therefore render the speech of the schizophrenic person inexact and vague.

Woods states that the language of the schizophrenic patient does not suffer from true agrammatism or from intrinsic disorders of language function. Ellipse seems to be the kernel of the language disturbance. Because of the disregard for the listener's understanding, schizophrenic language ceases to be a medium of exchange and becomes the content of thought. Schizophrenic thought, so highly subjective and expressed so arbitrarily in egocentric forms of speech, bewilders the listener who is thinking objectively. Woods emphasizes that the quality and final product (language) of thought association cannot be divorced from the affect or from the evaluation of the aptness of the product. Properties of thought association are in themselves, therefore, probably not the new and fundamental disturbance in schizophrenia, which is probably some other affective process, of which egocentricity is a manifestation.

MACKAY, Chicago.

ABSENCE OF GRIEF. HELENE DEUTSCH, Psychoanalyt. Quart. **6**:12, 1937.

In the process of mourning the libido invested in the lost love object is gradually withdrawn and redirected toward living persons and problems. The death of a beloved person must produce reactive expression of feeling, but the expression may become abnormal either through excess or through apparent absence.

Normal mourning may be excessive for the following reasons: 1. There has persisted a high degree of ambivalence toward the lost object. The more rigorous the early attempts to overcome inimical impulses the greater will be the difficulties encountered in the retreat from the ultimately achieved position. 2. There are strong feelings of guilt. Here, the reaction to death is greatly intensified, assuming a brooding, neurotically compulsive, even melancholic, character, sometimes culminating in suicide. 3. Normal mourning may be replaced by a state of severe anxiety due to a regressive process.

Absence of the mourning process also occurs. The absence is only apparent because the expression occurs in some other way.

Children often seem indifferent after the death of a loved person. This has been explained by the child's intellectual inability to grasp the reality of death and the inadequate formation of object relationships in early childhood.

Deutsch adds another explanation: The ego of the child is not sufficiently developed to bear the strain of the work of mourning and utilizes some mechanism of narcissistic self protection to circumvent the process. If the integrity of the ego is threatened by grief two courses are open: (1) regression to infantile anxiety and (2) mobilization of defense forces to protect the ego from anxiety. Absence of affect is the most extreme expression of this reaction.

Deutsch believes that the process of mourning as a reaction to the real loss of a loved person must be carried to completion. If the affect is excluded, the quality of painful reaction intended for the neglected direct mourning must be mastered. In cases in which the emotion is rejected or displaced there seems to be an awareness by the ego that it is unable to master the emotion and so defenses must be used.

PEARSON, Philadelphia.

THE UNWILLING PATIENT: A SYMPOSIUM. DENIS CARROLL, W. H. DE B. HUBERT, J. R. REES and O. H. WOODCOCK, Brit. J. M. Psychol. **17**:54, 1937.

Carroll gives a clinical classification of conscious unwillingness and then discusses the problem as it appears among groups of delinquent offenders. The dangers that arise from the frequent identification of the therapeutist with court groups are emphasized, and ways of avoiding them are suggested. Nevertheless, certain patients cannot be treated without coercion, and of this group a certain number respond. Carroll discusses the types in which he believes a "radical cure" may be hoped for with long psychoanalysis, but admits that such treatment is often difficult with suitable public safeguards. Shorter methods which may produce social stability are then indicated.

Hubert uses the homosexual person as a type of the unwilling patient and discusses a number of the reasons that treatment has no fundamental appeal to such a patient. He believes that a more complex definition of the problem may overcome the unwillingness by "allowing the patient the possibility of avoiding the direct issue."

Rees points out that the nonjudicial and nonmoral attitude is the first factor of therapeutic value, because it immediately arouses in the patient a sense of something different and the beginnings of an interest in his own behavior. The therapeutist hates the asocial acts of the patient, but not the patient himself. He believes "it is possible in the majority of cases . . . to enlist his interest in the problem of treatment, even though the first phase of treatment may have to be a sentence."

Woodcock illustrates with cases the following ways in which unwillingness may manifest itself in a patient: denial of guilt, sulkiness, indifference, extreme talkativeness and overcooperation.

ALLEN, Philadelphia.

THE RELATIONS BETWEEN DISSOCIATION AND REPRESSION. W. MCDOUGALL, Brit. J. M. Psychol. **17**:141 (March) 1938.

McDougall believes that concepts both of dissociation and of repression are necessary but that dissociation is sometimes confused with disintegration. A common assumption is that dissociation involves some kind of impairment or blocking of neural cross connections and that the unity of consciousness depends on neural continuity. However, McDougall finds necessary a fourth kind of functional relation between various parts of the total structure of the mind, namely, relations of dominance and subordination, making of it a unity in the sense of a hierarchical system, integrating and harmonizing the whole organization. These are strictly dynamic relations between the monads of the mind. Dissociation is failure or imperfection of the associative mechanism or structure, while conflict and repression are affairs of the dynamic or moral relations between units. Disorders may thus be of four kinds: (1) There may be mere loss of contact without conflict; (2) a unit may oppose order, causing conflict without loss of contact; (3) its opposition may be overwhelmed by superior moral force, repression; (4) such suppression may result in breakdown of communications, repression leading to dissociation.

ALLEN, Philadelphia.

THE ANALYSIS OF TEMPERAMENT. CYRIL BURT, Brit. J. M. Psychol. **17**:158 (March) 1938.

Burt obtained physical measurements and assessments of temperament of 124 London children referred for delinquency and neurotic difficulties and investigated the current classification of temperamental types by statistical methods. Covariances and correlations were calculated for eleven "primary emotional traits," such as anger, assertiveness, sexual propensities, tenderness and sorrow. Apart from the element of general emotionality, two bipolar factors appeared. The first indicated a general trait or tendency which predisposed people, when positive, to assertive, angry, sociable, inquisitive or aggressive conduct and, when negative, to submissiveness, fear, sorrow, tenderness and disgust—in a word, to repressive or inhibitive emotions. Others have pointed out similar antitheses, such as James's "explosive" and "obstructed" types and the "extrovert" and "introvert" of Jung. The second factor was positively weighted for pleasurable emotions, such as joy, tenderness and curiosity, and negatively weighted for unpleasant emotions, such as anger, sorrow, disgust and fear. As for physical measurements, small positive correlations were found between the temperamental and the physical factors, confirming to some extent the conclusions of Kretschmer and still more those of the Italian school.

ALLEN, Philadelphia.

ON THE OBJECTIVITY OF THE PSYCHO-ANALYST. J. H. VAN DER HOOP, Brit. J. M. Psychol. **17**:201 (March) 1938.

By what standards does one judge a candidate to be sufficiently analyzed for objective analytic practice? This is left to the intuition of the training analyst, an almost subjective standard of objectivity. Science strives for objectivity and theoretically should be ruled by thinking, rather than feeling, people. If this is applied to psychology, the analyst should be a thinking rather than a feeling person, but then he may not understand feelings. Lack of imagination and a fixed attitude in the ego hinder the understanding of others. Intuition and the growth of the human personality may compensate for this one-sidedness. The intuitive person is better able to understand persons different from himself.

Besides working with egoreactions, the psychotherapist may need to attack the authority of the superego. The ideally objective analyst may not want to influence ideals, but the ideally rational patient is rare, and ideals are usually kept safe from the influence of reason. Suggestion is a necessary factor in overcoming a rigid attitude, and the analyst cannot help showing his attitude by his silences as well as his words, ruled either by his unconscious reactions or by his ideals. In relation to ideals, the good form of objectivity is characterized by respect, by trying to understand the intentions of the other person; the bad form is characterized by conceit, by comparing ideals intellectually and proclaiming their relativity. It then seems possible to be beyond ideals. In problems of morality, most analysts take the stand that every one should find his own way to salvation. In such cases it might be safer for the patient to make sure his analyst shares his religious and political opinions and speaks the same language of ideals.

Objectivity in the field of psychology does not mean the ruling out of subjectivity. It implies being open to all possible forms of subjectivity, having experienced in oneself the sins of mankind as well as its highest aspirations and being aware of the different ways in which the ego tries to harmonize these influences. The study of the superego is beginning to trace the meaning of different ideals in various phases of life.

ALLEN, Philadelphia.

THE PSYCHO-ANALYTICAL FACTOR IN HYPNOSIS. N. SPEYER and B. STOKVIS, Brit. J. M. Psychol. **17**:217 (March) 1938.

Speyer and Stokvis attempt to secure further insight into hypnosis by phenomenologic examination, the person hypnotized trying to express his experiences in

words immediately after waking up. The subject was a man physician who had some acquaintance with psychoanalytic opinions and hypnosis. First he was hypnotized by a woman physician, with seven protocols, and then by a man physician, with eight protocols. Although the situation of hypnosis appeared complicated, the following conclusions were drawn: (1) The erotic attitude of the subject toward the hypnotizer plays an important role in establishing the hypnosis; (2) during hypnosis regression of the erotic instinct life takes place, sometimes to very early phases and generally reaching the stage of the Oedipus mechanism. In these protocols there seemed to be reactivation of the castration complex. The subject showed a masochistic attitude, strongly tinged with homoerotic tendencies toward the male hypnotist, as compared with a clearly heterosexual attitude toward the woman physician.

ALLEN, Philadelphia.

SCHIZOPHRENIA-LIKE PSYCHOSES IN YOUNG CHILDREN. R. A. Q. LAY, J. Ment. Sc. **84**:105 (Jan.) 1938.

Lay reports 6 cases in children between 3 and 5 years of age whose behavior seemed to place them in the group with dementia infantilis. In 4 of the cases the picture corresponded to that of dementia infantilis; in 1 the disease was obviously epidemic encephalitis, and in 1 there was a hyperkinetic syndrome. The prognosis is poor in all cases except those of the hyperkinetic syndrome. Differentiation of the syndrome is difficult and treatment ineffective.

KASANIN, Chicago.

METHOD OF STORY COMPLETION FOR DETECTION OF AFFECTIVE COMPLEXES AND CONFLICTS IN CHILDREN. M. THOMAS, Arch. de psychol. **26**:209 (Dec.) 1937.

Thomas criticizes the two methods now used by a majority of medicopedagogic counselors; namely, the method of direct interview and that of psychoanalysis. In her opinion, the former arouses considerable resistance on the part of the child, while the latter takes too much time to permit effective use. The method suggested by Thomas consists of a battery of short stories to be completed by the child. The underlying assumption is that each child is likely to consider the story, of the type selected for this method, in the light of his or her own emotional conflicts and complexes, thus enabling the examiner to detect both the source and the causes of the trouble. The application of the method to two groups of children showed that (1) in 90 per cent the results were in complete agreement with the actual situations of the subjects involved; (2) in 3.6 per cent the results did not seem to be substantiated by the facts, and (3) in 6.4 per cent it was impossible to secure definite pictures for the children studied.

GOBEY, Philadelphia.

SCHIZOPHRENIFORM PSYCHOSES IN CHILDHOOD. G. LANGFELDT, Encéphale **1**: 183, 1937.

In a group of 40 children hospitalized in a psychiatric service the condition of four was diagnosed as schizophrenia. The ages varied from 12½ to 15 years. Two were boys and two girls. One was an imbecile. One had presented hysteriform manifestations before the onset of schizophrenia, and one had always had a tendency to autism. Only 1 had hallucinations. The dominant clinical features were stereotypy, autism and anomalies of affectivity. Delusions of influence, of derealization and of depersonalization were not observed. There was no schizoid heredity. Psychogenic factors were believed to be the main causes in the present cases. The absence of depersonalization is explained by the incomplete development of the feeling of personality in children, as in mentally deficient persons.

LIBER, New York.

Meninges and Blood Vessels

PROLONGED MENINGOCOCCEMIA. ARTURO CARBONELL and EUGENE P. CAMPBELL, Arch. Int. Med. **61**:646 (April) 1938.

Carbonell and Campbell report 3 cases of meningococcemia in which meningitis developed, in one thirty-three days and in another forty-three days after the onset of symptoms; in the third case meningitis did not develop, and the patient recovered from the illness seventy days after its inception. In the 33 cases compiled from the American literature, the average age of incidence was 27.7 years, with extremes of 8.5 and 48 years. Twenty-three of the patients were male. Nineteen, or 57.5 per cent, of the patients did not have meningitis. The onset in the majority of the patients occurred within one or two days and was characterized by headache, chills, fever, rash and pains in the muscles and joints. During the first week an intermittent type of fever was present, similar in many respects to tertian or quartan malarial fever. The patient usually felt fairly well between the paroxysms. Progressive secondary anemia, common with other types of septicemia, was rarely encountered. The average duration of the disease was twelve weeks. There were 3 deaths, 2 of them occurring after the onset of meningitis. Endocarditis and hemiplegia have been reported during the disease.

BECK, Buffalo.

SUBUNGUAL NEUROMYO-ARTERIAL GLOMUS TUMOR OF THE TOE: EFFECT OF INCREASED PERIPHERAL TEMPERATURE. FRANK V. THEIS, Arch. Surg. **34**:1 (Jan.) 1937.

Theis reports a case of subungual neuromyoarterial glomus tumor of the toe occurring in a patient suffering from senile arteriosclerotic peripheral circulatory disease. Histologic examination confirmed the diagnosis of a glomus tumor. The tumor was not discovered until the development of an excruciating painful crisis and exquisite tenderness of the toe. These symptoms followed improved circulation produced by treatments with alternating positive and negative pressure. In more than 1,400 patients with peripheral circulatory disease treated with alternating positive and negative pressure no other glomus tumor was observed. In no other case of glomus tumor reported has a similar study of peripheral temperatures been made.

GRANT, Philadelphia.

GONOCOCCIC MENINGITIS. S. E. BRANHAM, R. H. MITCHELL and W. BRAININ, J. A. M. A. **110**:1804 (May 28) 1938.

Of 500 cultures sent to Branham, Mitchell and Brainin during the last two years to be typed for meningococci, the organism in 10 (or 2 per cent) was found to be the gonococcus; one half of these cultures, or 1 per cent, were of spinal fluid, and the other 1 per cent, of blood. A complete detail of the history was not available in some of the cases, but it is definitely known that in 5 instances the infection of the meninges or blood stream followed gonococcic infection of the genital tract. It is usually assumed that meningitis due to the gonococcus is secondary to gonococcic infection elsewhere. But in 2 of 4 patients who were observed by the authors, neither evidence nor history of other gonococcic manifestation was obtainable. Both these patients were young women—the gonococcus was considered a potential cause of primary meningitis both in the case described and in the other, that of a nurse who had what seemed to be primary gonococcic septicemia without meningeal involvement. It seems likely that gonococcic meningitis is much more common than is usually supposed. Hospital laboratories are usually too busy to carry identification of the causative micro-organism to completion, and a gram-negative coccus of typical morphologic character which occurs intracellularly and extracellularly in the spinal fluid and is agglutinated by antimeningococcus serum is usually assumed to be a meningococcus. Even when the study is carried further, definite criteria for the identification of the gonococcus are not well established, and its diagnosis is not easy. An absolute criterion is

lacking. Nevertheless, a careful study of cultures with consideration of all their characteristics—type of growth, form of colonies, fermentation reactions, solubility in alkalis and serologic reactions—will make an experienced worker sure of the identity of the strain in question. EDITOR'S ABSTRACT.

FATALITY RATES IN CEREBROSPINAL MENINGITIS. G. WALSH, J. A. M. A. **110**: 1894 (June 4) 1938.

In order to obtain light on the wide variability of the fatality rates in cases of cerebrospinal meningitis, Walsh addressed letters to a number of the health departments of the larger municipalities, since information obtained from these sources would be compiled without prejudice. He records the experience of 24,000,000 urban dwellers with epidemic cerebrospinal meningitis for sixteen years (from 1920 to 1936). The fatality rate in different municipalities varied from 67.7 to 38.1 per cent. The average fatality rate was 51.2 per cent. It is difficult to estimate the fatality rate of the disease before the use of serum. The fatality rates recorded by Flexner (1913) apparently referred to one or more epidemic outbreaks of the disease. On one point all observers have agreed: The death rate varies greatly from year to year. Several clinicians of wide experience have expressed the opinion that the fatality rate in the preserum era varied from 20 to 80 per cent. Rosenau listed about 6,000 cases occurring in New York state during the years 1904 and 1905, with a fatality rate of 51+ per cent. The fatality rate defined in this contribution approximately equals that recorded by Rosenau. It is Walsh's opinion, from the available evidence, that the treatment of epidemic cerebrospinal meningitis as used in the urban population described over the period to which he refers has reduced the fatality rate of this disease little, if at all. The failure of the fatality rate to decline, as has been the case in most infectious diseases during this period, suggests that the type of treatment referred to may have harmful rather than beneficial effects. This view of the question is of sufficient import to invoke earnest and careful study. EDITOR'S ABSTRACT.

DURAL SINUS THROMBOSIS IN EARLY LIFE: I. CLINICAL MANIFESTATIONS AND EXTENT OF BRAIN INJURY IN ACUTE SINUS THROMBOSIS. O. T. BAILEY and G. M. HASS, J. Pediat. **11**:755 (Dec.) 1937.

Bailey and Hass correlate the extent of brain injury with the localization of the thrombi in the venous sinuses and their tributary veins in 80 cases of thrombosis of the dural venous sinuses in children, all but 3 of whom were less than 3 years of age. Especial attention is given to the large group of infants and children in whom the thrombosis could not be attributed to the localization of a demonstrable infectious agent in the wall of the sinus or the tributary veins. In 42 children thrombosis was associated with various forms of sepsis: meningitis, scalp infections, otitis media, mastoiditis and bacteremias without meningeal localization. In 4 instances it followed surgical procedures. Thirty-three patients presented no evidence of infection of the central nervous system or blood stream. They were all infants less than 30 months of age. The illness began with an acute nutritional disturbance and was usually followed after a period of days or weeks by evidences of meningeal irritation, marked hyperpyrexia and convulsions or other abnormal neurologic manifestations. Some infants died without any evidence of neurologic disturbance. In all these patients the superior longitudinal sinus was thrombosed in its entirety or in part, with variable involvement of other sinuses and cerebral veins. Twenty-one of the patients presented hemorrhages into the meninges, 19 of whom had associated intracerebral hemorrhage and necrosis. Some of the patients succumbed within a few hours after the onset of the symptoms referable to involvement of the central nervous system. A few lived for from ten days to one month. Finally, 2 patients recovered from their acute attacks and died later with organized and canalized thrombi in the superior longitudinal sinus. EDITOR'S ABSTRACT.

CASE OF STREPTOCOCCAL MENINGITIS TREATED WITH PRONTOSIL. I. VITENSON and G. KONSTAM, Lancet **1**:870 (April 10) 1937.

Vitenson and Konstam report the case of a boy aged 10 with streptococcic meningitis complicating acute otitis media who was treated with sulfanilamide and one of its derivatives in addition to orthodox surgical measures. The patient gave a history of otitis media on the left side, of three weeks' standing. For nine days he had had mucopurulent otorrhea, without pain or tenderness over the mastoid. On the tenth day there suddenly developed a temperature of 104.6 F., without any exacerbation of the aural symptoms. A Schwartze operation performed on the left side revealed extensive osteitis of the mastoid process with pus and granulations in many cells. The lateral sinus was not exposed, and the lamina of bone covering it was apparently normal. Seven days after operation the temperature became normal; the wound was healing satisfactorily, and the aural discharge had ceased. On the twelfth day after operation the patient awoke with severe generalized headache, photophobia, vomiting and a temperature of 104.1 F. Kernig's sign, with slight rigidity of the neck, was present, and the margins of the optic disks were blurred. The cerebrospinal fluid was under pressure and contained 3,690 cells, the majority of which were pus cells. Cocci were seen in films; on culture there proved to be hemolytic streptococci. On the same evening the wound was reopened, and Neumann's operation for meningitis was performed. On the day after the second operation the patient was delirious and by evening had sunk into deep coma. The temperature became normal twenty days after the second operation, and progress after that was uneventful. Postoperative treatment consisted of daily lumbar puncture for thirteen days and the administration of 10 cc. of prontosil soluble (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′-,6′-disulfonic acid) parenterally, twice a day, and 2 tablets of sulfanilamide orally, twice a day. The cerebrospinal fluid became sterile on the seventh day, and the cells fell to 35 per cubic millimeter thirteen days after operation.

WATTS, Washington, D. C.

INFLUENZAL MENINGITIS IN AN ADULT WITH RECOVERY. E. WATSON-WILLIAMS, Lancet **2**:1430 (Dec. 18) 1937.

Watson-Williams reports a case of meningitis due to the influenza bacillus in a woman aged 46, with recovery following frequent lumbar punctures and the intravenous administration of colloidal silver. The patient complained at first of severe pain in the left ear after a severe cold. This disappeared and she returned to work. Two weeks later there developed a temperature of 103 F., signs of meningeal irritation and absence of the knee jerk and plantar reflexes. Lumbar puncture showed turbid, greenish spinal fluid, which was under increased pressure, 94 per cent polymorphonuclear cells, no dextrose, 590 mg. of chlorides per hundred cubic centimeters, a total protein content of 180 mg. per hundred cubic centimeters and a pure growth of Bacillus influenzae. A proprietary preparation of colloidal silver (Collosol argentum) was given intravenously in doses of 30 and 50 cc. daily, accompanied by the withdrawal of from 20 to 80 cc. of spinal fluid. The day after the therapy was commenced, the spinal fluid was much thicker and became yellow. One week after the onset of the meningitis, the spinal fluid was "thick and chocolate colored," and the temperature was 99 F. In three weeks the drowsiness disappeared, and the patient was discharged a week later in "good general condition."

KRINSKY, Boston.

MENINGEAL REACTIONS TO SERUM. F. ROCCHI, Policlinico (sez. med.) **45**:187 (April 1) 1938.

Rocchi discusses the significance of the meningeal reactions which follow intraspinal injections of heterologous serum and the danger of the reactions which take place in the course of serotherapy for epidemic cerebrospinal meningitis. He

followed the meningeal reactions which took place in the course of intraspinal injections of heterologous serum in patients who were suffering from poliomyelitis, tetanus and meningococcic meningitis. The meningeal reaction takes place whether or not the meninges are inflamed. The reaction develops within twenty-four hours of the injection, reaches its greatest intensity in two days and diminishes or disappears in a week. Even though further intraspinal injections of serum are given, the reaction disappears. The meningeal reaction may include the appearance of clinical meningeal symptoms in association with changes in the cytologic reactions of the cerebrospinal fluid or only the latter. The cytologic reaction consists in predominant polynucleosis in the cerebrospinal fluid with a few histiocytes. The clinical symptoms and the colloidal reactions of the cerebrospinal fluid are of meningitic type. Glycorrhachia is normal. General symptoms of serum anaphylaxis may develop in the course of the reaction, but in all his experience Rocchi has never seen meningeal anaphylaxis. He classifies the meningeal reactions to intraspinal serum therapy as immediate (clinical and cytologic) and late (general or focal anaphylactic). He suggests the name "meningosis" for the meningeal serum reactions. The nature of this reaction, whether toxic or anaphylactic or showing aggravation of meningococcic or suppurative meningitis, can be ascertained by the cytologic picture of the cerebrospinal fluid. Polymorphonuclear leukocytes, which are in abundance in the cerebrospinal fluid during the meningeal reaction, are well preserved and stain normally when there is no meningitis. Pus shows in the cerebrospinal fluid with the Cesaris-Demel reaction when there is meningitis. The author concludes that toxic or anaphylactic reactions to serum do not develop as frequently as is believed and that fear of development of the reaction should not be an obstacle in administration of prolonged serum treatment of epidemic cerebrospinal meningitis.

EDITOR'S ABSTRACT.

BILATERAL ANEURYSM OF THE INTERNAL CAROTID ARTERY. A. BOZZOLI, Riv. oto-neuro-oftal. **14**:304 (May-June) 1937.

Bozzoli reports a case of bilateral aneurysm of the internal carotid artery which produced optic neuritis bilaterally, erosion of the sella turcica and, in the latter part of the illness, an acromegalic syndrome. He points out the difficulty of making a diagnosis of aneurysm of the carotid artery during life and states that there is no way of distinguishing changes of the sella due to aneurysm except by roentgenologic visualization of the vascular lesions.

ALPERS, Philadelphia.

QUANTITATIVE INVESTIGATIONS ON THE CAPILLARY CONTENT OF THE CEREBRAL GRAY MATTER IN YOUNG AND IN AGED PERSONS. A. G. H. LINDGREN, J. f. Psychol. u. Neurol. **47**:492, 1937.

The capillary system in analogous portions of the brain of young and of old persons was examined. The length of the system was approximately the same in young and in old persons, as well as in patients with destruction of brain parenchyma from causes other than senile involution. This, according to Lindgren, indicates that the capillary content is closely related to the volume of the brain and, perhaps more closely, to its functional capacity. The process underlying reduction of the capillary system in the brain is apparently capillary fibrosis. The question whether in a given case reduction of the capillary content of the brain is secondary to that of the nerve elements in the cerebral substance or whether it is the primary factor in the process cannot as yet be determined.

KESCHNER, New York.

BRAIN ACTIVITY IN DOGS FOLLOWING REDUCTION IN THE CEREBRAL BLOOD SUPPLY. L. A. ANDREYEV, Arkh. biol. naouk **45**:203, 1937.

Andreyev reports the effect of experimentally induced acute and chronic anemia of the brain in 24 dogs. The changes in the circulatory system were studied by

the roentgenographic method. Andreyev first ligated both common carotid and both vertebral arteries simultaneously. About 40 per cent of the animals died within twenty-four hours after the operation with symptoms of acute bulbar anemia. When the ligation was performed at intervals of from ten to fourteen days the dogs survived, even when the ten chief arteries were ligated. After ligation of the arteries collateral passages developed. These were usually completed in from four to six weeks. After this came enlargement of the collateral passages and of the anastomoses, a process which lasted for a year or longer.

NOTKIN, Poughkeepsie, N. Y.

Diseases of the Brain

THE RELATIONSHIP OF SYDENHAM'S CHOREA TO OTHER RHEUMATIC MANIFESTATIONS. LUCY PORTER SUTTON and KATHERINE G. DODGE, Am. J. M. Sc. **195:** 656 (May) 1938.

Sutton and Dodge reach the conclusion, first, that most children with chorea are rheumatic and, second, that if this is not true there is no clinical means at present by which it is possible to differentiate a rheumatic from a nonrheumatic attack. The present study deals with the detailed records of 467 children who had chorea and were subsequently under observation in the clinic. Of 217 children suffering from their first attack of chorea, 149 (68.6 per cent) had had no recent previous illness or emotional upset, and 21 (9.6 per cent) had had a recent emotional upset. Of a group of 1,052 rheumatic patients, chorea was present at some time in 467 and absent in 585. Of the former group, frank rheumatic attacks occurred in 52 per cent, and muscle and joint pains, in 29.4 per cent, while 91 (19.9 per cent) had chorea only. Of the 91 patients, 17 (18.6 per cent) had organic heart disease at the end of a mean of four and eight-tenths years from the onset of the chorea. The child who begins his rheumatic career with chorea has a 50 per cent chance of acquiring heart disease. Chorea signifies to the authors that the patient has been attacked by the same infection which produces rheumatic heart disease. It does not mean that chorea causes heart disease.

MICHAELS, Boston.

HEADACHE FROM THE NASAL WALL. H. H. BURNHAM, Ann. Otol., Rhin. & Laryng. **46:**69 (March) 1937.

The source of headache or pain involving the trigeminus nerve in diseases of the nasal cavity is discussed. Burnham advances a hypothesis for the explanation of this headache or pain: 1. The irritation within the nasal mucosa from the products of bacterial invasion produces a hypersensitive or susceptible state. 2. As a result, substances normally produced in the tissues from external stimuli, such as changes of atmosphere or drafts, cause excessive stimulation of the neurovascular mechanism and sensory nerves. The headache or pain that results is in the nature of "referred pain" and involves one or more branches of the trigeminus nerve. 3. The "tender spot" beneath the nasal bridge is believed to be due to pressure from congestion on the trunk of a hypersensitive nerve (a branch of the anterior ethmoid) in a bony foramen or canal, and this, in turn, may aggravate or produce the headache or pain. The hypothesis applies to the pain associated with sinusitis. A cotton applicator introduced into the nasal cavity will indicate, as a rule, a hypersensitive condition of the mucosa. If the cotton is moistened with a 3 per cent solution of ephedrine in saline and applied to the middle turbinate bone, spectacular relief may be experienced by the patient in a few minutes. He will say in a surprised tone that "the headache is gone." The author made further search for tender spots, with the finding of an excessively tender spot just beneath the bridge of the nose. On passing a cotton applicator along the bridge of the nose in the narrow channel formed at the junction of the septum and the lateral

nasal wall, the patient experienced a sudden severe pain. In a few minutes, as a rule, great relief from the headache was experienced and the "spot" became less tender. This "tender spot" is situated over the course of the lateral nasal nerve, a branch of the anterior ethmoid nerve. Presumably, in these cases of headache, this nerve, or a branch of it, leaves the bony canal at this point and is subject to pressure from the vascular coat in the periosteum about it. The ephedrine causes contraction of the overlying veins and, presumably, those in the neighboring canal, and in this manner the pressure on the nerve is relieved. The result is often amazing and of diagnostic significance.

EDITOR'S ABSTRACT.

A STUDY OF MINERS' NYSTAGMUS. RAYMOND S. BROCK, Brit. M. J. **1**:443 (Feb. 26) 1938.

Brock observed 118 cases of miners' nystagmus in workers from fifteen coal mines in North Wales. The ocular movements were vertical, horizontal, oblique or rotatory. The average time of onset was twenty-three and three-tenths months. The nystagmus was definitely related to darkness and did not develop in well lighted mines. The condition was frequently associated with an anxiety psychoneurosis.

ECHOLS, New Orleans.

HUNTINGTON'S CHOREA: A STUDY OF THIRTY-FOUR FAMILIES. L. MINSKI and E. GUTTMANN, J. Ment. Sc. **84**:21 (Jan.) 1938.

Minski and Guttmann studied 34 families with Huntington's chorea, involving more than 300 persons, in an effort to determine whether the relatives showed neuropsychiatric disorders. The main motor characteristic of the relatives was general hyperactivity or restlessness. At first sight many of the relatives impressed the observer as having mild forms of chorea, but they were not considered to be such by other members of the family, who had seen real cases of the disease. Many of the relatives showing motor anomalies appeared to have a "psychopathic personality" characterized by irritability, quick temper, stubbornness, sensitiveness and a tendency to dominate. A few patients had introverted schizoid types of personality.

There were 25 cases of alcoholism in the authors' series, some of them occurring in patients in whom chorea subsequently developed and some in the relatives. Suicide, which was mentioned by Huntington as a frequent feature ot the disease, was not found to be common by Minski and Guttmann. The early symptoms were largely in the nature of changes in personality. They consisted of irritability, stubbornness, moodiness and quick temper. Depression was a frequent first symptom. In a few instances the patients were described as sensitive or paranoid.

KASANIN, Chicago.

CEPHALIC TETANUS. PAUL B. WILKINSON, Lancet **1**:753 (March 27) 1937.

Wilkinson reports the case of a youth aged 17 who slipped on a rock and fell head first down a small waterfall, but did not lose consciousness. On examination, two cleancut wounds 1½ inches (3.8 cm.) and ½ inch (1.27 cm.) long, respectively, were found on the scalp, over the left pterion and the parietal eminence. Probing revealed no evidence of fracture. The wounds were cleansed and sutured. Four days later the wound was infected, and staphylococci were observed in the pus. Ten days after the accident the right upper eyelid drooped, and the left half of the face was weak. On looking to the right the left eye did not cross the midline. There was no diplopia; all reflexes were normal and symmetric. Two days later a peculiar deviation of the eyes was noted; the right eye, the orbicularis palpebrarum muscle of which was in spasm, was directed downward and outward when the lid was raised, and the left eye, upward and outward. The left eye had full range of movement, but the right did not cross the midline on deviation to the left.

The patient now complained of stiffness in the left side of the face, which was still weak. The left masseter muscle was rigid on palpation; the right was normal. Tetanus was diagnosed, and 150,000 units of antitetanus serum was immediately given intravenously. Six hours after the injection the boy showed well marked opisthotonos and trismus, and speech had become typically tetanic. Numerous spasms developed, with marked opisthotonos and esophageal spasms and involvement of the bladder and bowel. Treatment consisted of large doses of magnesium sulfate intramuscularly and fluids as indicated. Recovery was complete.

Wilkinson attributes the recovery primarily to the good physique and youth of the patient, and secondarily to the short incubation period of six days. Magnesium sulfate given intramuscularly was of undoubted value in reducing the frequency of the generalized spasms and enabled tube feeding to be carried out when esophageal spasm made swallowing practically impossible.

WATTS, Washington, D. C.

HEMIPLEGIA IN DIPHTHERIA. PHILIP SCIENCE, Lancet **1**:779 (April 2) 1938.

Science reports the case of a boy aged 10 who presented hemiplegia during the course of diphtheria. Marked cervical adenitis was present, and petechiae were seen in the skin of the axilla and upper part of the chest. Twenty thousand units of diphtheria antitoxin was given intramuscularly on entrance to the hospital, on the fifth day of the illness, followed by a similar amount intravenously in a half-hour. The neurologic signs began on the eleventh day of the illness with palatal paresis, followed by pharyngeal weakness. During the third week, facial weakness of peripheral type was present on the right side, accompanied by absence of knee and ankle jerks. On the twenty-fourth day of the illness complete left hemiplegia was discovered, associated with peripheral neuritis of purely motor type. At this time extrasystoles were heard, and the heart tones were feeble. Slow improvement in the paralysis was noted in eight weeks, and after six months the patient was discharged with residual weakness of the left arm and leg, associated with spasticity and a Babinski sign on the same side. In the majority of cases reported, hemiplegia following diphtheria has occurred on the right; in this case it was on the left. The author suggests that the hemiplegia may have been due to emboli from thrombosis produced by the cardiac dilatation with enfeebled heart action and mobilized during the cardiac irregularity. He states that endocarditis never occurs in diphtheria.

KRINSKY, Boston.

TUMORS OF THE BASE OF THE BRAIN: THEIR RELATION TO PATHOLOGICAL SLEEP AND OTHER CHANGES IN THE CONSCIOUS STATE. L. B. COX, M. J. Australia **1**:742 (May 15) 1937.

Cox presents cases of tumor, unassociated with internal hydrocephalus, involving the midbrain and hypothalamic and thalamic regions; each was accompanied by certain changes in the conscious state. These changes included such phenomena as drowsiness and hypersomnia, trancelike conditions, periods of apathy, catatonic states, alterations in disposition, disorientation for time and place, marked loss of memory and mental excitement. In certain cases the removal of the tumor resulted in recovery from the abnormal mental state. An attempt is made to explain the conditions of lessened consciousness as disturbance of a sleep mechanism. A working hypothesis is formulated, based on the possible relation of sleep to an inhibitory process. The relation of conditions of exalted consciousness to excitation or release from control of mechanisms for the expression of the emotions is discussed. It is indicated that the region of the brain stem, hypothalamus and basal ganglia may be of importance in the better understanding of the problems of psychotic conduct.

EDITOR'S ABSTRACT. [J. A. M. A.]

SIGNIFICANCE OF RETINAL ARTERIAL HYPERTENSION IN CEREBRAL ANGIOSPASM. F. SCHOUSBOE, Ann. d'ocul. **174**:603 (Sept.) 1937.

In 43 per cent of 53 cases of cerebral lesions of angiospastic origin the condition was not accompanied by modification in the retinal circulation. In 57 per cent there was hypertension of the retinal arteries, which was transitory in 79 per cent and permanent in 21 per cent.

BERENS, New York.

UNUSUAL GROUPING OF SYMPTOMS IN A CASE OF ACUTE ENCEPHALITIS. M. LOEPER, A. LEMAIRE, L. ROY and LŒWE-LYON, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:548 (May 3) 1937.

Loeper and his associates describe the case of a young person who had hemiplegia of the left side with predominance of symptoms of crural involvement; the condition was slowly progressive and suggested a cortical lesion due to syphilitic arteritis. It began with lessening of the muscular force of the lower left extremity, predominating in the contractor muscles and distal parts. Gradually the upper left extremity and the facial nerve were affected. Lumbar puncture and a Wassermann test of the blood gave normal results. There was some central scotoma. About ten days later the symptoms became aggravated; the patient showed signs of meningitis; examination of the spinal fluid showed a high leukocyte count (from 300 to 400 per cubic millimeter), an albumin content of 0.85 Gm. per liter and a sugar content of 0.55 Gm. per liter. After a few days the meningeal symptoms disappeared, but the hemiplegia became spastic. The face was shiny, cold and expressionless; the patient remained without motion but was not lethargic. The paralysis was mainly functional, not unlike Parkinson's disease, in which the automatic reflexes were intact. The patient died with signs of bulbar paralysis: hiccup, respiratory asynchronism in the two halves of the thorax, frequent vomiting, rapid pulse and, finally, syncope. The authors state that the case was one of encephalitis based on a syphilitic disorder, although no syphilitic symptoms were discernible.

EDITOR'S ABSTRACT. [J. A. M. A.]

MENTAL DISTURBANCES IN CASES OF MENINGIOMA OF THE LESSER WING OF THE SPHENOID BONE. MARCEL DAVID and HARDEN ASKENASY, Encéphale **1**:169, 1937.

David and Askenasy report 26 cases of meningioma of the lesser wing of the sphenoid bone, in 22 of which mental disturbances were present. In 13 there was intellectual deterioration characteristic of that associated with a frontal lesion, consisting of confusion, lowering of intellectual level and changes in character. Patients often remained seated in one place for days. They were half somnolent, with expressionless faces. Answers to questions were slow and monotonous and occurred only after insistent and repeated questioning. All 13 patients had disturbances in memory. In 7 of these memory for recent facts alone was involved; in 6 there was amnesia for all events. In 2 cases of tumor on the left side the disturbances in memory at first involved only proper names. In 2 cases, in addition to disturbances in memory and disorientation, fabulation and false recognition gave a picture of Korsakoff's psychosis. Paradoxic euphoria occurred in several cases. Puerilism and mannerisms were present in 2 cases. Only in these 2 cases of more than 1,000 cases of tumor observed was definite puerilism shown. This suggests that simultaneous lesions of the frontal and temporal lobes may be the chief factor in producing puerilism. This is in keeping with Kennedy's hypothesis that the temporal lobe plays a preponderant part in the fixation of puerile memories. Stimulation of this region by a tumor produces the dreamy state, with sudden revival of early memories. David and Askenasy suggest that in their cases the recall of childhood memories was continuous, and not paroxysmal. Olfactory hallucinations occurred in 1 case. The odor was fetid and unlike anything known to the patient. Accompanying the hallucination were vertigo and pallor of the

face, but no loss of consciousness. The tumor in this case was medial and caudal, compressing the uncus. In another case the typical dreamy state, with intense visual and auditory sensations, was presented. The rostromedial portion of the temporal lobe was compressed by the tumor, removal of which was followed by disappearance of the dreamy state. Hallucinations occurred in only 8 per cent of cases of meningioma of the lesser wing, whereas Cushing observed unciform fits in 40 per cent of 59 cases of glioma of the temporal lobe. In the 2 cases of this series the hallucinations were the first manifestation of the tumor. In other cases there were syndromes similar to schizophrenia, manic-depressive psychosis or psychasthenia, or only mild confusion or slight somnolence. In addition to the direct local effect of the tumor, diffuse changes, such as cerebral edema and ventricular dilatation, play a part in the genesis of the mental disorders.

LIBER, New York.

DISORDERS IN CONDUCT IN CASES OF TUMOR OF THE BRAIN. MAX DE CRINIS, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:426 (Nov.) 1937.

De Crinis reports 2 cases of tumor of the brain in which antisocial behavior and unethical conduct dominated the clinical picture. The first case was that of a man aged 38 who became slower and less interested in his work, with transitory episodes of confusion. He began to masturbate openly, even in the presence of women. He was dull, euphoric and without insight. There was some awkwardness of movement and ataxia of the trunk, as well as dyspraxia. A glioma originated in the corpus callosum and extended into the left frontal pole. The second case was that of a man aged 33 who showed inability to handle money which he collected as a streetcar conductor. For the first time in thirteen years, he had two accidents. He was discharged from work because of inefficiency. Changes in personality had been present for more than six months. The optic disks were pale. There were bilateral central scotomas, and the posterior clinoid processes were eroded. The patient complained of defective vision and occasional weakness on the left side. Hyposmia was found bilaterally. There was no intellectual defect. Autopsy revealed a meningioma arising from the tuberculum sellae and extending forward and compressing the frontal lobes. In both cases there were marked disturbances in conduct leading to antisocial acts, indicating failure of previously intact inhibitory processes. In neither case were there striking mental changes or intellectual defects. The frontal lobes were affected in both cases, especially at the base of the brain. Kleist and Spatz had already called attention to the significance of the orbital surface of the frontal lobe for the more highly integrated psychic functions.

SAVITSKY, New York.

Diseases of the Spinal Cord

A CASE OF CONGENITAL NEUROSYPHILIS, AGED SIXTY YEARS, WITH MULTIPLE OSTEOARTHROPATHIES. WILLIAM C. MENNINGER and CARROLL C. CARLSON, Am. J. Syph., Gonor. & Ven. Dis. **22**:327 (May) 1938.

Menninger and Carlson report a case of congenital neurosyphilis in a woman aged 60, in which the disease resembled dementia paralytica of tabetic type. The history and clinical manifestations indicated that the patient, a virgin, suffered from congenital syphilis. Symptoms appeared before her twentieth year, but she did not have antisyphilitic treatment until she was 30. Treatment was irregular and inadequate because of the patient's mental attitude. At the age of 43 there developed rapidly progressive involvement of the vertebrae, which was diagnosed as a Charcot joint. A similar disturbance occurred in the right hip a short time later. The spinal fluid obtained by cisternal puncture when the patient was 54 showed 2 cells per cubic millimeter, a positive Nonne reaction, a negative complement fixation reaction and a colloidal gold curve of 0000332100. At 60

she presented evidence of dementia paralytica of tabetic type. The Kahn reaction of the blood was doubtful, and the quantitative Kolmer test gave normal results. The spinal fluid contained 3 cells per cubic millimeter, the Kahn, Eagle and Wassermann reaction were negative, and the colloidal gold curve was 0000011000.

BECK, Buffalo.

CURIOUS ILLUSTRATION OF "MASS REFLEX" AND INVOLUNTARY MICTURITION FOLLOWING INJURY OF THE SPINAL CORD. O. R. LANGWORTHY, Bull. Johns Hopkins Hosp. **60**:337 (May) 1937.

Langworthy discusses the case of a young woman who sustained an injury of the lower lumbar portion of the spinal cord. Reflex micturition finally became established. Impending micturition produced flexion of the toes bilaterally, adduction of the right foot and extension and internal rotation of the legs. These movements were associated with cramplike pain in the urethra and contracted muscles. Holding the toes extended postponement of micturition. Voiding could be induced by stimulation of the perineal region. The contraction of the muscles illustrates the sacral reflex.

EDITOR'S ABSTRACT. [J. A. M. A.]

SCIATIC SCOLIOSIS. E. N. WARDLE, Lancet **1**:749 (March 27) 1937.

Wardle tabulates and divides a series of 26 cases of sciatic scoliosis into two broad types, those of sciatic pain and obvious scoliosis and those of sciatic pain in which a slight degree of lateral deviation of the spine became apparent during examination. The clinical observations in these cases oppose the theory that sciatic scoliosis is due to arthritis of the lumbar intervertebral joints, mainly on the ground that true arthritis should produce complete limitation of movement; it is unlikely that the symptoms would always be unilateral if arthritis were present; if such arthritic edema were causing pain by compression of nerve roots, it is extraordinary that the fourth and fifth lumbar roots appear to be the only ones ever affected. The direction of the deformity may be significant in elucidating the cause of this condition, for there are two possible explanations of the spasm and deformity of the muscles. Irritation of the affected nerve roots by pressure could produce muscle spasm reflexly on the same side of the body as the pain, and, second, an involuntary effort on the part of the patient to relieve pressure by opening up the neural foramen on the affected side would produce contraction of the muscles on the side of the body opposite that of the pain—a contralateral deformity.

EDITOR'S ABSTRACT.

INJURIES OF THE SPINAL CORD FOLLOWING DIAGNOSTIC PROCEDURES. R. DONAT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:34, 1937.

In 2 patients the use of lumbar anesthesia was followed in several months by sensory disturbances in the lower extremities and incontinence of urine and feces. Death was due to uremia following ascending urinary infection. The changes in the spinal cord simulated those of syphilis, although both patients had a negative Wassermann reaction. The main alterations involved the leptomeninges and were of a chronic productive and inflammatory nature. The leptomeninges were adherent to the dura dorsally from the middle of the thoracic region caudally. The nerves of the cauda equina were converted into a bundle adherent to the dura and pia. Dorsally, in the regions most severely involved, all three coverings of the cord were thickened and converted into a connective tissue sheath. The picture was typical of chronic pachymeningitis and leptomeningitis with atrophy and necrosis of the spinal nerve roots. The explanation of these untoward effects following lumbar anesthesia is not clear. There is a possibility that the anesthetic was the injurious agent. Therefore the solution one uses should be fresh. Another possibility is that there was preexisting inflammation of the coverings of the cord. A third is that infection was introduced through a technical error.

A pathologic condition similar to the one described was noted after the use of iodized sesame oil in myelographic examination. The leptomeninges were slightly thickened anteriorly, and yellow-brown streaks of the oil were observed in them. Near the collections of iodized oil were areas of granulation tissue. The process increased in severity from above downward. In a chemical investigation of iodized sesame oil and of iodized poppyseed oil, it was found that the stimulant action is not dependent on the iodine contents of these preparations. The oil in which the iodine was dissolved contained unsaturated fatty acids; when the solutions aged their free fatty acid content increased. The free fatty acids were regarded as the substances causing lesions when injected into the spinal subarachnoid space.

RUKSTINAT, Chicago. [ARCH. PATH.]

Peripheral and Cranial Nerves

ELECTROCARDIOGRAPHIC CHANGES AND PERIPHERAL NERVE PALSIES IN TOXIC DIPHTHERIA. EDWARD A. BURKHARDT, CARY EGGLESTON and LAWRENCE W. SMITH, Am. J. M. Sc. **195**:301 (March) 1938.

This study was an attempt to correlate the cardiac changes as determined by clinical observation, serial electrocardiograms and autopsy. Of 140 patients with toxic diphtheria, only 28 showed electrocardiographic evidence of cardiac damage. In 23 patients changes in the T waves occurred between the fifth and the thirty-ninth day of the illness. Seventeen patients showed changes in conduction between the fifth and the thirteenth day; in 11 of these patients auriculoventricular dissociation developed. This complication invariably proved fatal. Palsies of peripheral nerves occurred in 17 (74 per cent) of the 23 patients showing changes in the T waves. The average time of onset was the twenty-third day. Paralysis occurred in 10 (59 per cent) of the 17 patients showing changes in conduction. Many patients showing clinical nerve palsies have accompanying toxic myocarditis. The essential histologic changes in the myocardium due to toxic diphtheria, as demonstrated in the 7 autopsies, were progressively, edema, congestion, cellular infiltration, degenerative changes in the muscle fibers and ultimate fibrosis.

MICHAELS, Boston.

MERALGIA PARAESTHETICA: REPORT OF 150 CASES. A. D. ECKER and H. W. WOLTMAN, J. A. M. A. **110**:1650 (May 14) 1938.

Ecker and Woltman review the present status of meralgia paraesthetica and analyze the clinical observations in 150 cases studied under standard conditions for a moderately long time at the Mayo Clinic. The incidence of the condition was 0.035 per cent, or about 3 in 10,000 of the clinic population. This figure can be compared with 0.94 per cent, or 4,293 cases of sciatica, and with 1.16 per cent, or 5,316 cases of other forms of peripheral neuritis recorded during the same period. Meralgia paraesthetica is neuritis of the lateral femoral cutaneous nerve, which is caused usually by pressure or tension on the overlying fascia, but occasionally is caused by other factors. It most commonly affects obese, middle-aged men and usually begins as a sense of numbness over the anterolateral aspect of one thigh. Later, to the numbness are added the sensations of burning, tingling and pain, which are aggravated by standing or walking. Both thighs may be affected. Usually there can be found slight loss of appreciation of light touch, pain and thermal sensation in the affected area. It is important to recognize the condition in order to exclude the presence of a specific causative factor and then to reassure the patient that the discomfort is usually self limited and that, if necessary, it can be relieved by simple severance or resection of the lateral femoral cutaneous nerve.

EDITOR'S ABSTRACT.

PRESSURE ON BRACHIAL PLEXUS CAUSING SIMULATION OF CORONARY DISEASE. W. D. REID, J. A. M. A. **110**:1724 (May 21) 1938.

Reid observed a series of patients in whom the pressure of a cervical rib or the scalenus anticus muscle on the brachial plexus had been the cause of pain simulating angina pectoris. These diagnoses differ significantly in prognostic and therapeutic implications. The syndrome has been found in the absence of a cervical rib; an abnormality in the relation of the first rib and the brachial plexus is the cause. The syndrome has been explained as due to friction neuritis; the nerves are made taut across the sharp edge of the rib as the result of various unfavorable conditions in the relations of the nerves to the bony structures. More recently, attention has been directed to the effect of the scalenus anticus muscle in causing pressure on the subclavian artery or brachial plexus or both. The scalenus anticus muscle may compress the artery or nerves against the cervical rib, if such is present, or it may abnormally elevate the first rib and so interfere with the artery and plexus. If the latter is irritated the scalenus anticus muscle, which receives its innervation from the brachial plexus, may be stimulated to a state of spasm. A "vicious cycle" may be said to exist. The important part played by the scalenus anticus muscle and the fact that it may cause symptoms identical with pressure by a cervical rib, in cases in which there is no extra rib, are the justification for the term "scalenus anticus syndrome." Pain, paresthesia and anesthesia in the area supplied by the affected nerve are the usual symptoms. The pain is neuralgic in character: It may begin in the neck and spread downward along the arm to the hand and sometimes in the reverse direction to the head and side of the chest. Rotation of the head toward the affected side or a downward pull on the shoulder may increase the pain. Loss of or decrease in amplitude of the radial pulse and a bruit over the clavicle are other symptoms and signs that may be noted. The simplest form of treatment is that of elevation of the shoulder upward and backward by a sling. Physical therapy is then used in an attempt to develop the trapezius and levator anguli scapulae muscles. If such measures prove unsuccessful and the symptoms warrant it, surgical treatment is advised. Operations are described for removal of the cervical rib or first rib, whichever is the cause of the pressure on the brachial plexus or subclavian arteries. A considerable number of patients have been relieved by section of the scalenus anticus muscle without removal of the bone.

EDITOR'S ABSTRACT.

MULTIPLE PERIPHERAL NEUROPATHY VERSUS MULTIPLE NEURITIS. I. S. WECHSLER, J. A. M. A. **110**:1910 (June 4) 1938.

Wechsler believes that the whole concept of multiple neuritis is in need of revision and that the term as used in most cases now so designated is a misnomer. In the vast majority of cases, whether the condition is due to a toxin, a foreign poison or avitaminosis, there is a degenerative and not an inflammatory process. It is suggested that the term multiple neuropathy, polyneuropathy or peripheral neuropathy be substituted for multiple neuritis in the cases in which both the cause and the pathologic changes point to a degenerative process and that the designation neuritis be retained only in cases in which there is adequate causation and in which an inflammatory condition is recognized as well as demonstrable. The nomenclature will then conform to that now employed in the case of the brain and spinal cord, namely, neuropathy, encephalopathy and myelopathy.

EDITOR'S ABSTRACT.

LANDRY'S SYNDROME AND SYPHILIS. HENRI ROGER, JEAN PAILLAS and JEAN VAGUE, Encéphale **1**:47, 1938.

The authors report 2 cases of syphilis associated with Landry's syndrome. The first case was that of a man aged 49 in whom there suddenly developed

marked difficulty in moving the legs. The next day walking was almost impossible, and urination and defecation were difficult. Two days later the upper extremities were paralyzed. Nine days after the onset, paralysis had involved the muscles of mastication and deglutition. Retention of urine became complete. There were tingling and dragging pains in the legs. The knee and ankle jerks were absent, and there was a Babinski sign on the right. The deep reflexes were present in the arms. The Wassermann test of the blood was positive. The spinal fluid contained 38 lymphocytes per cubic millimeter and 150 mg. of protein per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was strongly positive. Treatment with mercury, arsenic and bismuth compounds was followed by regression of the paralysis, in the inverse order of its appearance, in the course of several weeks. After nine months there remained only slight fatigue after walking, slight dysuria and a Babinski sign bilaterally. This case was considered to be one of Landry's syndrome, due to syphilis. The second case was that of a man aged 47 who was alcoholic and for a year and a half had suffered from dyspepsia, with loss of weight. The syndrome began with paresthesias in both legs, ascending in four or five days to the arms. After this, complete flaccid paraplegia appeared, with retention of urine and intense constipation. The movements of the arms were limited, and there were intense crushing pains in the arms. The Wassermann test of the blood was positive, and that of the spinal fluid was negative. The paralysis progressed to complete tetraplegia. Hiccup and buccal spasms with periods of apnea lasting several seconds were present. On the thirty-fifth day there was slight improvement, but on the fortieth day the patient died of acute respiratory failure, in spite of antisyphilitic treatment. In this case, the Landry syndrome was believed to be of nonsyphilitic origin, although it occurred in a syphilitic patient.

LIBER, New York.

ETIOLOGIC BASIS OF THE SYNDROME OF GUILLAIN AND BARRÉ. A. BIEMOND, J. belge de neurol. et de psychiat. **38**:231 (March) 1938.

Biemond observed 10 patients with the syndrome of radiculoneuritis accompanied by albuminocytologic dissociation in the cerebrospinal fluid. All the patients presented symptoms of acute or subacute polyneuritis, with both motor and sensory changes in the upper and lower extremities; bilateral facial palsy was observed frequently. Electrical examinations in most cases showed a complete reaction of degeneration. Examination of the cerebrospinal fluid showed an increase in the albumin content, at times xanthochromia, but little increase in cells. The condition is said to be caused by a neurotropic virus, as yet unknown. It frequently follows various infections, such as enteritis and nephritis. In 1 of the author's cases it occurred with toxemia of pregnancy; in other cases it was associated with bronchopneumonia, peritonsillar abscess, pulmonary tuberculosis and carbon monoxide intoxication. Pathologic examination in cases of radiculoneuritis shows no changes of consequence. There is some edema of the nerves and roots and congestion of the arachnoid, but little infiltration. Biemond believes that these changes are toxic in origin and that at present there is no conclusive evidence that the disorder is caused by any known neurotropic virus.

DE JONG, Ann Arbor, Mich.

COLOCYNTH POLYNEURITIS. FRIEDRICH WILHELM KROLL, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:422 (April) 1938.

Kroll reports a case of polyneuritis limited to both lower extremities, more marked in the right, in a woman aged 51 who had been taking a preparation of colocynth in alcohol, 3 teaspoonfuls (12 cc.) a day, for a year. The complaints were numbness and pain in both lower extremities, of eight days' duration, and rapidly increasing paralysis of both lower limbs, of five days' duration. The clinical findings were those of involvement of the lower motor neuron with sensory

changes in the distribution of the peripheral nerves in the legs. There were no mental changes. The condition cleared up in about four months. While the preparation taken by the patient contained about 35 per cent of alcohol, Kroll believes that the alcohol played only an accessory role in the production of the neuritis. He believes that the chief etiologic factor in this case was colocynth.

SAVITSKY, New York.

Vegetative and Endocrine Systems

PITUITARY BASOPHILISM OF CUSHING—SYNDROME OF THE BASOPHILE ADENOMA. I. PARDEE, Bull. Neurol. Inst. New York **6**:183, 1937.

The outstanding signs of basophilism are plethora, acrocyanosis, petechiae and purpuric spots, associated at times with polycythemia, and a remarkable cutaneous manifestation which takes the form of purplish red striae extending radially from the pubes over the abdomen and horizontally or vertically over the hips and thighs. This syndrome was described by Cushing in 1932. Pathologic study of the anterior lobe of the hypophysis in a group of cases of this disorder showed the presence of a basophilic adenoma. The syndrome occurs also with adenoma of the adrenal cortex. In many cases of typical pituitary basophilism an adenoma or hyperplasia of the adrenal cortex had been observed. Study of the anterior lobe of the hypophysis as a routine has shown the existence of basophilic adenoma in the absence of the clinical picture of basophilism.

Pardee analyzes the symptoms and pathologic changes associated with basophilism in relation to the glandular functions of the anterior lobe of the pituitary and the adrenal gland. Adiposity, sexual dystrophy, osteoporosis, the occasional symptoms of polyphagia, polydipsia and polyuria, a high cholesterol content of the blood and low sugar tolerance with hyperglycemia are considered to be due to a primary disturbance of the pituitary. Hypertrichosis, virilism and sexual precocity are attributed to disturbances of the adrenal. Hypertension is considered a possible manifestation of pathologic changes in either gland. Bauer's opinion that the presence of osteoporosis is indicative of primary disease of the pituitary is considered important in the differential diagnosis. The syndrome is of pluriglandular origin, and the pituitary exerts a primary influence, with secondary hyperfunction of the adrenal, thyroid and parathyroid glands.

Hyaline changes in the basophilic cells of the pituitary are considered significant, since this change was common in the pituitary gland in cases of basophilism and was not observed in cases of basophilic adenoma in which the clinical syndrome of basophilism was absent.

KUBITSCHEK, St. Louis.

THE SITE OF FORMATION OF THE POSTERIOR LOBE HORMONES. C. FISHER, Endocrinology **21**:19 (Jan.) 1937.

Fisher has collected evidence that the pars nervosa is necessary for elaboration of the hormones of the posterior lobe of the hypophysis. Lesions in the anterior part of the hypothalamus interrupting the supraopticohypophysial tracts resulted in degenerative changes in the pars nervosa of the hypophysis and the supraoptic nuclei of the hypothalamus. Extracts were prepared from the hypophyses of 5 normal adult cats and from the atrophic glands of 4 adult cats with diabetes insipidus. The action of the pars intermedia was excluded by proper tests. Fisher concludes that the absence of pressor, antidiuretic and oxytocic activities in the hypophyses of cats is correlated with degeneration of the pars nervosa and that the latter must play a role in the elaboration of these components.

PALMER, Philadelphia.

ALTERATIONS IN THE PERCENTAGE OF CELL TYPES IN THE HYPOPHYSIS BY GONAD TRANSPLANTATION IN THE RAT. C. A. PFEIFFER, Endocrinology **21**:812 (Nov.) 1937.

Cytologic differences between the hypophyses of male and those of female rats have been reported. Previous work by Pfeiffer showed that the pituitary gland is undifferentiated at birth and that the type of differentiation depends on the sex. The testis dominates this differentiation if both a testis and an ovary are present in the same animal. The present investigation was undertaken to correlate physiologic activities with the cytologic character of the hypophysis and to demonstrate whether a hypophysis which is experimentally altered in its physiologic reactions shows corresponding changes in the cell types. Male castrated albino rats with ovaries transplanted in the neck at birth, or in the eye at puberty, had the female type of pituitary gland both in physiologic response and in cell counts. The sexual predominance was especially evident in the low eosinophilic cell count. However, the basophilic cells varied a great deal with the state of the graft. If females were castrated at birth and received grafts of a testis at this time the histologic pattern of the hypophysis after puberty was that of the male. Genetic females castrated either at birth or at puberty and grafted with ovaries produced the female cell pattern of the pituitary gland. Genetic males castrated at birth and grafted with testes had the male cell pattern of the pituitary gland. However, if both a testis and an ovary were present in the same animal, regardless of its genetic sex, the tendency was to form the male pattern. There was a definite pattern in the hypophysis of the rat which was distinct for each sex, and each pattern was represented by characteristic percentages of the various cell types. Both the physiologic and the histologic character may be altered within the limits of this pattern, but attempts to alter the pattern after the pituitary gland has become completely differentiated have thus far been unsuccessful.

PALMER, Philadelphia.

CYTOLOGIC EVIDENCE OF THE GONADOTROPIC ACTIVITY OF THE RABBIT'S ANTERIOR HYPOPHYSIS. H. B. FRIEDGOOD and A. B. DAWSON, Endocrinology **22**:674 (June) 1938.

Physiologic evidence shows that a rapid functional change takes place in the anterior lobe of the hypophysis of the rabbit within the first few hours after mating. The authors attempted to determine whether recognizable cytologic changes occur in the gland coincident with this period of secretory activity. Cytologic observations were made as controls on the pituitary glands from seven groups of animals in order to evaluate any changes which might occur subsequent to mating. Experimental observations were made on a series of 50 animals at frequent intervals after mating, beginning at thirty minutes after coitus and extending throughout the period of pregnancy (thirty days). The pituitary glands of 3 pseudopregnant and of 3 male animals were studied for comparison with those of the females. Sixty-one animals serving as controls were compared with the experimental series of 53 females. Only 6 of the 61 control animals showed well circumscribed, conspicuous areas of large, densely stained carmine cells. There were no large carmine cells among the castrated animals and the immature does. On the other hand, all the 23 animals on which autopsy was performed between forty-five minutes and eight hours after coitus showed histologic evidence of activation. The reaction was strongest from one to three and a half hours after coitus; after this, degranulation occurred, and the carmine granules were isolated, smaller and much less conspicuous. These data reveal a parallelism between the gonadotropic activity of the anterior lobe of the hypophysis and the presence of the activated form of the carmine cell. Isolated small carmine-staining cells can be seen in the pituitary glands of castrated and immature rabbits. Their number appears to be increased in animals approaching sexual maturity and may occasionally be fairly prominent in the pituitary gland of the estrous rabbit. These cells dominate the cytologic

appearance of the gland only after mating and become markedly enlarged and increased in number. It is known that within from one to two hours after coitus the blood stream receives enough gonadotropic hormone from the anterior lobe of the pituitary to produce ovulation and the carmine cell is a prominent feature of the microscopic picture of the gland. The precise relation to the pituitary hormones which are known to be secreted at this time is as yet not clear.

PALMER, Philadelphia.

PSEUDOHERMAPHRODITISM, ADIPOSITY, POLYURIA AND HYPERGLYCAEMIA: AN INFUNDIBULO-TUBERIAN SYNDROME. R. M. STEWART, J. Neurol. & Psychiat. **1**:68 (April) 1938.

Stewart reports the case of a boy aged 17 years who was normal at birth, except for external pseudohermaphroditism, and acquired in his third year marked obesity and retardation of growth and intelligence, with typical features of adiposogenital dystrophy. Later, polyuria, polydipsia, excessive somnolence and hyperglycemia developed. There were severe chronic degenerative changes in the hypothalamic nuclei, especially in the nucleus supraopticus, nucleus tuberis lateralis, nucleus tuberomamillaris, nucleus paraventricularis and the substantia grisea of the third ventricle. The cellular loss was most marked in the tuberal and paraventricular nuclei and was less evident in the nucleus tuberomamillaris. The nerve cells of the nucleus supraopticus were less altered, but both here and in the nucleus paraventricularis there was intense gliosis. According to Stewart, the clinical picture was conditioned not by alterations limited to the pituitary gland but by disturbance of the reciprocal interactions between the pituitary and the hypothalamic nuclei which regulate its activities. Because of the diffuseness of the lesions, it was difficult to determine the more exact location of the structures responsible for the individual symptoms.

MALAMUD, Ann Arbor, Mich.

MENTAL DISORDER IN CUSHING'S SYNDROME. W. S. MACLAY and A. B. STOKES, J. Neurol. & Psychiat. **1**:110 (April) 1938.

Maclay and Stokes emphasize the importance of recognizing mental states associated with Cushing's syndrome. They report the case of a young woman in whom during four years there developed the signs characteristic of Cushing's syndrome, associated with severe mental reactions. The mental symptoms could be divided into: (1) emotional reactions to the illness, such as irritability, seclusiveness, depression and suicidal ideas, and (2) organic manifestations, consisting of episodes of confusion, excitement and paranoid delusions. The latter could be attributed to the hypertension or to the systemic disturbances resulting in altered function of the brain. It was difficult to establish a causal relation between the endocrine disorder and the psychologic symptoms. Pathologically, the most diagnostic observation was the hyaline change in the cytoplasm of the basophilic cells in the pituitary gland. It was difficult, however, to explain the great paucity of the basophilic cells. No tumors were observed in any of the endocrine organs, but there were diffuse hypertrophy of the adrenal cortex and atrophy of the sex organs.

MALAMUD, Ann Arbor, Mich.

TUMOR GROWTH IN HYPOPHYSEAL DWARFISM. BERNHARD ZONDEK, Lancet **1**:689 (March 20) 1937.

In previous papers Zondek has shown that it is possible to produce dwarfism experimentally in rats by the prolonged administration of estrogen, which prevents the growth hormone elaborated in the anterior lobe of the pituitary from entering the blood stream. The absence of the growth hormone is shown by the fact that rats so treated grow more slowly and cease growth earlier than normal. That the dwarfing is hypophysial in origin may be deduced from the finding that Evans'

growth hormone from the pituitary stimulates the dwarf animals to grow again. Ball and Samuels observed a less pronounced growth of mammary carcinoma transplanted in hypophysectomized albino rats. Reiss, Druckrey and Hochwald stated that if a rat weighing from 60 to 120 Gm. is inoculated with Jensen sarcoma two or three weeks after hypophysectomy the tumor will grow to the size of a pea and will then undergo complete involution. This effect is lacking even if the slightest remnant of tissue of the anterior lobe of the pituitary is left during extirpation.

Zondek reasons that if the growth of malignant tumors depends on the growth hormone of the anterior lobe of the pituitary one would expect that malignant tumors would not grow—or at least would grow much more slowly—in hypophysial dwarf rats than in rats used as controls. For the experimental tumor Zondek used the sarcoma induced by injection of benzpyrene, as described by Kennaway and Cook and others. The experiments were carried out in 2 male dwarf rats and 2 male rats used as controls. The experiments were repeated in 2 female dwarf rats and 2 female rats used as controls. Zondek found that the tumors grew as fast in dwarf rats as in the animals serving as controls. He concludes that the absence of growth hormone in the dwarf rats does not impede the growth of malignant tumors. From this it follows that the growth hormone of the anterior pituitary has no important effect on the growth of malignant tumors.

WATTS, Washington, D. C.

THE HYPOPHYSIS AND WATER EXCHANGE. P. W. WERMER, Wien. Arch. f. inn. Med. **32**:189 (April 30) 1938.

Wermer discusses recent advances in knowledge of the pathogenesis of diabetes insipidus, giving special attention to the significance of the anterior lobe of the hypophysis in the pathologic and physiologic relations of water exchange. After pointing out that the significance of the anterior lobe of the hypophysis in diabetes insipidus was indicated two decades ago by the observations of von Hann, he cites recent observations, particularly by American authors, which likewise indicate that the anterior lobe plays a part. On the basis of these reports in the literature and of his own experiments and observations, he reaches the conclusion that a substance with strong diuretic action can be extracted from the anterior lobe of the hypophysis. This substance is contained in the fraction which also contains the growth hormone. There are two types of diabetes insipidus: that caused primarily by the posterior lobe of the hypophysis and that caused by the anterior lobe. In both types there exists a disproportion between the diuretic hormone of the anterior lobe of the hypophysis and the antidiuretic hormone of the posterior lobe of the hypophysis. The deficiency in secretion of the posterior lobe of the hypophysis may be caused by destruction of the posterior lobe or by impairment of its innervation. An excess of hormone of the anterior lobe of the hypophysis may be caused by a basophil adenoma or during pregnancy by a transformation of the hypophysis which is elicited by the genital glands. Destruction of the anterior lobe of the hypophysis in the presence of an unimpaired posterior lobe produces oliguria; however, if it is accompanied by destruction of the posterior lobe, the development of diabetes insipidus is prevented.

EDITOR'S ABSTRACT.

Cerebrospinal Fluid

THE RELATION BETWEEN PLASMA AND CEREBROSPINAL FLUID CALCIUM. A. T. CAMERON and V. H. K. MOORHOUSE, J. Physiol. **91**:90, 1937.

The ratio of calcium of the cerebrospinal fluid to that of the serum in 24 dogs with a normal calcium content of the blood averaged 50 per cent. Results of experiments following injection of calcium salts or of parathyroid extract, with

or without continuous open drainage from the cisterna magna, lead to the conclusion that the cerebrospinal fluid calcium represents the diffusible fraction of the plasma calcium only when the calcium content of the blood is normal.

McCouch, Philadelphia.

The Intracranial Pressure During Barbital Narcosis. J. Stephen Horsley, Lancet **1**:141 (Jan. 16) 1937.

In a series of 100 cases, Horsley finds that a striking contrast is presented by the raised intracranial pressure of natural sleep and the lowered pressure during barbital narcosis. In each case lumbar puncture was performed with the patient in the left lateral position and the head supported at the same level as the lumbar portion of the spine. Pressures were measured with a vertical glass tube manometer fitted to a special needle. Each observation was continued for from one-half to three hours, and the readings were plotted on a graph at intervals of thirty seconds. The punctures were performed without an anesthetic, except in the case of certain apprehensive patients who received a local injection of nupercaine. In many cases there were initial fluctuations in pressure from changes in postural tension. For this reason, narcosis was not induced until the pressure in the manometer became steady. The solution of barbital was then injected by the accepted technic until the onset of unconsciousness.

The effect of narcosis was an abrupt fall in the cerebrospinal fluid pressure to about half its previous level. This fall either preceded or accompanied loss of consciousness. It was constant and indicative of full narcosis. A cautious overdose produced a more profound fall of pressure, reaching zero in many cases; in 2 cases negative pressures were shown. Conversely, administration of a subhypnotic dose of barbital failed to produce any significant change in the cerebrospinal fluid pressure. In most cases the pressure rose slowly during narcosis, but failed to reach its original level until the return of consciousness. In more than half the cases there was a distinct second fall at the moment of waking. These effects are common to various barbitals—pentobarbital sodium, evipan (a sodium salt of n-methyl-C-c-cyclohexamylmethyl barbituric acid), pentothal sodium (sodium ethylmethylbutyl thiobarbiturate), pentothal and soneryl sodium (a sodium salt of butylethyl barbituric acid). The findings were constant in 99 per cent of the cases. They were present with full narcosis and were absent with subhypnotic doses of barbital.

Watts, Washington, D. C.

Overbreathing Tetany: Changes in the Calcium of Serum, Serum-Ultrafiltrates, and Cerebro-Spinal Fluid. R. A. McCance and E. Watchorn, Lancet **1**:200 (Jan. 23) 1937.

The chemical changes in the blood, urine and cerebrospinal fluid during tetany produced by overbreathing have been extensively investigated. Barnes and Greaves found a fall in the calcium content of the cerebrospinal fluid during tetany. Since McCance and Watchorn considered it improbable that the amount of calcium in the cerebrospinal fluid is reduced in tetany caused by overbreathing, they repeated this work under rigid experimental conditions with 2 women, of whom 1 suffered from severe attacks of tetany brought on by hysterical overbreathing and the other was normal. They found that spontaneous overbreathing sufficient to cause severe tetany brought about a rise in the serum calcium and a slight rise in the ultrafiltrable calcium but no change in the calcium or phosphorus content of the cerebrospinal fluid. Although susceptibility to alkalosis tetany varies from one person to another, a high degree of susceptibility is compatible with a normal life, and the ease with which tetany can be induced has no diagnostic significance.

Watts, Washington, D. C.

THE CEREBROSPINAL FLUID IN SPONTANEOUS OVERBREATHING TETANY. J. N. CUMINGS and E. A. CARMICHAEL, Lancet **1**:201 (Jan. 23) 1937.

Recently, Barnes and Greaves (1936) discussed the role of calcium in tetany associated with spontaneous overbreathing and recorded cases in which there was a fall in the calcium content of the cerebrospinal fluid during tetany. They suggested that this fall was associated with alkalosis, with consequent lowering of the diffusible calcium of the blood, which was immediately reflected in the calcium content of the cerebrospinal fluid. Cumings and Carmichael studied the calcium content of the cerebrospinal fluid and the blood serum of 2 patients with tetany produced by spontaneous overbreathing. In neither was there any appreciable decrease in the calcium of the cerebrospinal fluid, although a small decrease was found in the serum calcium.

WATTS, Washington, D. C.

THE CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS. H. DIBBERN and B. ROPERS, Deutsche Ztschr. f. Nervenh. **144**:81, 1937.

Dibbern and Ropers found abnormalities of the cerebrospinal fluid in 94 per cent of 77 cases of multiple sclerosis. The total protein was increased in 70 per cent, and qualitative tests gave positive results in an additional 14 per cent; the colloidal gold reaction was abnormal in 80 per cent, and the cell count was moderately increased in 26 per cent. There was dissociation between the total protein content and changes in the colloidal gold curve in 30 per cent of cases of multiple sclerosis, as compared with 7 per cent of cases of various other conditions. This dissociation is of diagnostic importance in clinically suspicious cases of multiple sclerosis, if syphilis can be excluded. The authors were unable to find any relationship between the abnormalities in the cerebrospinal fluid and the clinical condition of the patient or the prognosis.

MERRITT, Boston.

VITAMIN C IN THE SPINAL FLUID DURING HUNGER. MICHIO KASAHARA, TAKAO KASAHARA and MINORU HORIE, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:529 (Jan.) 1938.

The vitamin C content of the spinal fluid was studied in dogs, cats and monkeys. Dogs and cats are known to be able to synthesize their own vitamin C. In 8 dogs the vitamin C content of the spinal fluid was determined before and after various periods (from three to twelve days) of absolute fasting. No alteration in the vitamin C content of the spinal fluid was found in any of the cats or dogs after fasting. Eight monkeys were studied in similar fashion after from two to twenty days of fasting. In monkeys there was a gradual decrease in the vitamin C content as the fasting continued. Just before death the vitamin C values were approximately one-fourth the normal figures.

SAVITSKY, New York.

Treatment, Neurosurgery

CLINICAL INDICATIONS FOR ANTERIOR PITUITARY-LIKE SEX HORMONE. R. L. SCHAEFER, E. A. SHARP and J. V. LAMMY, Endocrinology **22**:643 (June) 1938.

The authors treated 16 male patients with genital hypoplasia and crytorchidism and 15 females with amenorrhea and 13 with menometrorrhagia with appropriate endocrine products. The results were uniformly good. For the 16 patients with genital hypoplasia and cryptorchidism the results of treatment with the anterior pituitary-like gonadotropic principle from the urine of pregnant women were gratifying. The authors believe that surgical intervention is indicated only when failure of descent after adequate treatment with the gonadotropic substance has been demonstrated or in the presence of a demonstrable anatomic condition which must be corrected by surgical procedure. The authors believe also that if the patient's progress is checked from time to time by roentgenographic studies of osseous

development there is no danger of producing premature sexual development and early epiphysial closure. The folly of pursuing a course of nonintervention in cases of cryptorchidism and genital hypoplasia is stressed. Of the 16 patients, 14 showed adiposogenital pituitarism and responded favorably to treatment. The patients with amenorrhea ranged in age from 13 to 28. The duration of the amenorrhea varied from two months to four years; 4 of the patients presented typical adiposogenital pituitarism. They were treated with a combination of theelin (estrone) and the gonadotropic substance. The latter was given for two weeks immediately after a period of bleeding and during the two weeks preceding the expected menstrual period; theelin was given as a replacement agent. All patients in this group showed satisfactory response to treatment in the establishment of a menstrual cycle. The patients with menometrorrhagia, ranging in age from 20 to 47 years, were treated with the gonadotropic substance. In 6 of the 13 patients the response to treatment was satisfactory. For 4 patients, whose ages ranged from 40 to 47 years, larger doses of the gonadotropic substance were given, with varying effects.

PALMER, Philadelphia.

FOLLOW-UP REPORT OF NINETY-NINE CHILDREN WHO RECEIVED FEVER THERAPY FOR CHOREA. L. P. SUTTON and K. J. DODGE, J. Pediat. **12**:490 (April) 1938.

Sutton and Dodge compare the results in 99 children who were given fever therapy for chorea with those in 60 children who did not receive this treatment. All these patients were seen in the first attack, most of them during recurrences. The first group was composed of 48 treated and 23 untreated patients, for whom the period of observation was from one to three years. The second group consisted of 51 treated and 37 untreated patients observed from four to six years. The most striking difference was the higher incidence of polyarthritis and death from heart disease among the untreated patients in both observation periods. None of the treated patients observed from one to three years had aortic lesions, whereas 1 of the untreated patients did. In the group observed from four to six years aortic disease developed in 1 treated patient, as compared with 6 in the untreated group. That is, of those who had organic heart disease in the group observed from one to three years none of the treated patients had aortic disease, as compared with 16.66 per cent of the untreated group. In the group observed from four to six years 6.66 per cent of the treated group who acquired heart disease had aortic lesions as compared with 46 per cent of the untreated group. If these observations are valid, the reason may be that the infectious process is inhibited by fever. If fever therapy modifies the course of rheumatic infection, it is a far more important therapeutic procedure in this disease than if its value is confined to shortening an attack of chorea.

EDITOR'S ABSTRACT.

THE TREATMENT OF EPILEPSY WITH PSYCHOSIS BY PROMINAL [MEDARAL]. D. E. SANDS, J. Ment. Sc. **83**:703 (Nov.) 1937.

Sands treated 66 patients suffering from epilepsy complicated by a psychosis with medaral (n-methylethylphenylmalonylcarbamide), a drug which is closely related to phenobarbital. Three grains (0.195 Gm.) of medaral are equivalent to 15 grains (0.975 Gm.) of potassium bromide and 1½ grains (0.097 Gm.) of phenobarbital. The author used 3 grains (0.195 Gm.) a day for the mild forms and 6 grains (0.39 Gm.) for the more severe. In all patients but 3 there was definite diminution in the number of fits. Psychotic patients with epilepsy in the more advanced stages were not benefited by this treatment. In cases in which milder degrees of mental disorder were shown, medaral was of definite benefit.

KASANIN, Chicago.

A Comparison of Insulin and Cardiazol Convulsion Therapies in the Treatment of Schizophrenia. H. P. Strecker, Lancet **1**:371 (Feb. 12) 1938.

Strecker recommends the combined use of insulin and metrazol in treatment of patients with schizophrenia who have failed to improve with insulin hypoglycemia alone. The mortality was extremely low with experienced workers in both types of therapy—1 per cent for 700 patients receiving insulin and 0.5 per cent for 600 patients given metrazol. Cardiovascular collapse, laryngeal spasm and other complications occurred less frequently with "convulsive therapy." The unpleasantness of treatment with metrazol could be alleviated by giving a combination of morphine, scopolamine and atropine half an hour before the injection. Both groups of patients gained weight. The recoveries obtained in the clinics at Budapest, Hungary, and Vienna, Austria, have persisted even after four years. Relapses occurred in from 6.5 (Müller) to 15 per cent (Frostig) of patients given insulin and in 23 per cent of those given metrazol (Angyal and Gyárfás). Poor results or relapses may often be due to errors in technic. The largest percentage of complete or incomplete remissions was obtained in both types of therapy with illnesses lasting one year or less. In this group the incidence of improvement reached as high as 60 per cent. Briner found improvement in 9 per cent of 54 patients whose illness was of more than five years' duration. Forty per cent of 495 patients with disease of about two years' duration who were treated with insulin had complete or incomplete remissions (Müller). There were remissions in 37.4 per cent of 265 patients treated with metrazol (Meduna, Briner, Angyal and Gyárfás).

Krinsky, Boston.

Muscular System

Choline Esterase Activity in Disease, with Special Reference to Myasthenia Gravis. Murray McGeorge, Lancet **1**:69 (Jan. 9) 1937.

McGeorge studied the esterase activity of the serum of 132 patients, including 3 with myasthenia gravis. Wide variations were found, and no correlation with the type of disease or with other factors could be established. The 3 patients with myasthenia gravis showed esterase activity of the serum of 1.9, 2.6 and 4.4 units —i. e., well within the normal range—with little variation on repeated examination from day to day. After the administration of a therapeutic dose of 3 mg. of prostigmine, however, there was a sharp drop in esterase activity to from one-third to one-half that of the resting level with gradual restoration during the succeeding four or five hours, toward the end of which period myasthenic symptoms returned. These patients remained "strong" only during the period of artificial depression of the esterase level and relapsed as this returned to the previous value. In a similar experiment in which a dose of 2.5 mg. of prostigmine was administered to each of 3 nonmyasthenic patients, a corresponding depression of esterase activity to approximately one third of the resting level again occurred, accompanied in from ten to fifteen minutes by severe visceral and tonic skeletal muscular activity. The tonic contraction of skeletal and visceral muscles is due presumably to prolonged stimulation by acetylcholine on artificial depression of the esterase. Depression of esterase activity of the serum by prostigmine is due to inhibition, not destruction, of the esterase, since activity is restored on removal of prostigmine by dialysis. It is McGeorge's opinion that myasthenia gravis is associated with a failure of equilibrium between the rate of liberation of acetylcholine at the motor end plates and the rate of its destruction by the esterase locally present. There is, however, no proof that the esterase activity of the serum is a measure of the concentration of esterase at the motor end plates, a factor which at present cannot be measured.

Watts, Washington, D. C.

A Case of Dystrophy Intermediate Between the Syndrome of Apert and That of Hurler. Gilbert Muyle and Ludo van Bogaert, Encéphale **2**:169, 1937.

A man aged 36 was institutionalized for mental deficiency and epilepsy. No cases of mental defect or of dystrophy were found in his family. With a Terman test the intelligence rating was 6 years and 10 months. The patient was loquacious, hypomanic, puerile and excessively suggestible. There were scoliosis, posterior acrocephaly and ultrabrachycephaly. The fingers and toes presented a certain degree of syndactyly. The patient was amblyopic and had coarse horizontal nystagmus. The pupillary light reflex was absent. The eyegrounds showed simple atrophy of the optic nerve and chorioretinitis bilaterally. The external auditory canals were narrowed. The blood pressure was 200 systolic and 50 diastolic. Roentgenographic examination showed thinning of the calvarium, with a distinct and widened coronal suture, shortening of the anterior fossa, dilatation of the sella, marked prognathism and spina bifida occulta in the lumbar region. There were ankylosis of the elbows and shoulders, genu recurvatum, spontaneous subluxation of the interphalangeal joints, retraction of the left hand and abnormal laxity of the ligaments of the knee. There was spastic paraplegia. The condition in this case is intermediate between Apert's acrocephalosyndactyly and Hurler's syndrome. The latter consists of dwarfism, cranial hyperostosis, dehiscence of sutures, kyphosis, hyperostosis of the scapula and acromion, retraction of the fingers, corneal opacity, marked mental deficiency and anatomic changes similar to those in juvenile amaurotic idiocy (Hurler, G.: Ztschr. f. Kinderh. **24**:85, 1919. Tuthill, C. R.: Juvenile Amaurotic Idiocy: Marked Adventitial Growth Associated with Skeletal Malformations and Tuberculomas, Arch. Neurol. & Psychiat. **32**: 198 [July] 1934). The tentative conclusion is that these conditions may all be related to the diseases of lipid metabolism and not to teratologic defects, as was heretofore believed.

Liber, New York.

Unilateral Predominance of Caloric and Optokinetic Nystagmus in a Case of Myasthenia. A. Franceschetti and E. Barbey, Rev. d'oto-neuro-opht. **15**:669 (Dec.) 1937.

The question whether myasthenia is of central or peripheral origin has been much discussed. Porta and Della Vedova observed a case of myasthenia in which optokinetic nystagmus appeared without latency, and when the direction of rotation was changed the nystagmus changed its direction immediately. A patient who had suffered from myasthenia, disequilibrium and bilateral ptosis for the preceding fifteen years was subjected to vestibular examination. With the cold caloric test in the left ear there was predominance of nystagmus to the right; with the warm caloric test in the right ear the predominance was also to the right. Similar predominance of nystagmus to the right was observed after the rotation test. These results indicate a pontile and bulbar localization of the myasthenic troubles. Recently, Scheinker observed at autopsy perivascular epitheloid infiltrations in the bulb and pons in a case of myasthenia.

Dennis, San Diego, Calif.

Diagnostic Methods

Cutaneous Histamine Reaction as Test of Peripheral Nerve Function. L. H. Loeser, J. A. M. A. **110**:2136 (June 25) 1938.

During the last three years Loeser has found the histamine test to be of value along the following lines: 1. Determination of the presence of degeneration, and later regeneration, in peripheral nerves following injury. Traumatic lesions to peripheral nerves, sufficient in extent to interrupt the integrity of the nerve, will abolish the flare reaction after from six to eight days. The absence of the flare

reaction frequently precedes the electrical reaction of degeneration by several days. Conversely, the flare begins to return in the area supplied by the regenerating nerve considerably earlier than the electrical reactions begin to change. 2. Differentiation of hysterical and organic anesthesia. In certain cases hysterical anesthesia closely simulates organic anesthesia, and even the expert occasionally finds the problem perplexing. The histamine test in which from six to eight days is allowed to elapse for degeneration is an effective method in this group of cases. The test is also of value in the cases in which actual organic anesthesia is present with superimposed hysteria. The test provides an accurate method of delimiting the true extent of anesthesia and is obviously independent of the patient's subjective response. 3. Differentiation of the anesthesias of malingering from the organic forms. The problem here is similar to that in hysteria. The histamine test demonstrates in a convincing manner the absence or presence of true dermal anesthesia. 4. As an additional aid in the localization of lesions of the spinal cord. In expanding lesions and in some compressing lesions of the spinal cord there is occasionally interference with the function of the ganglion of the posterior root. If two or more ganglia are involved, a segmental area of the skin at the upper level of the lesion will give a negatvie response to histamine. 5. Differentiation of involvement of the nerve roots and that of the spinal cord. The histamine reaction is negative (no flare) in the anesthetic area when the lesion involves the nerve roots but is normal if the anesthesia is the result of injury to the spinal cord. 6. Determination of the presence or absence of anesthesia of peripheral nerve origin when normal areas are used as controls, particularly in cases in which a negative reaction on one side can be compared with a positive reaction on the opposite side. The histamine reaction is a reliable and simple procedure to test the function of peripheral nerves and, as such, should be more widely utilized.

EDITOR'S ABSTRACT.

Cerebellum and Brain Stem

ATAXIA AND ASTEREOGNOSIS OF BULBAR ORIGIN. M. DAVID and H. ASKENASY, Brain **60**:354, 1937.

Lesions of the medulla oblongata frequently produce dissociation of sensation in which sensibility to pain and temperature is chiefly affected; this usually results from a lesion in the retro-olivary reticular substance, the vascular supply of which is derived from the posterior and inferior cerebellar arteries. Tactile and deep sensations are less frequently disturbed. This type of dissociation can be produced only by a small lesion involving the arcuate fibers of the bulbothalamic tract, which pass from the nuclei of Goll and Burdach to the piniform decussation, or by a lesion of these nuclei. In this case there is ataxia of movement due to disturbance of deep sensation.

Ataxia resulting from disorders of sensation has rarely been observed in cases of tumors of the medulla or of the fourth ventricle, and only exceptionally in those of other disturbances. It has not been reproduced experimentally. This syndrome has certain features in common with tabes dorsalis, such as the presence of ataxia and disorders of deep sensibility, but it is distinguished by normal tendon reflexes. The syndrome was observed by David and Askenasy in the course of the removal of a hemangioblastoma of the medulla oblongata. A woman aged 29 was admitted to the hospital with symptoms of increased intracranial pressure and disorders of equilibrium. Neurologic examination revealed nothing abnormal. Ventriculographic studies revealed a tumor of the posterior fossa. Operation disclosed a cystic tumor, with a mural nodule, of the left cerebellar lobe. The mural nodule and the membrane of the cyst were removed. Another similar tumor was observed occupying the midline, inserted on the posterior aspect of the medulla oblongata, about 8 mm. below the calamus scriptorius. This tumor was carefully removed. A third, but much smaller, tumor was observed on the lateral aspect of the

medulla oblongata at its junction with the spinal cord. No attempt was made to remove this tumor because of its vascularity. Pathologic examination of the tumor tissue disclosed a capillary hemangioblastoma. On the second day after operation the patient complained of an intense sensation of formication all over the body and of inability to localize the position of the limbs. There was no paralysis, but there was marked disturbance of stereognosis and of the sense of position. The responses to the cerebellar tests were poor on both sides. About a month later it was found that the patient was unable to walk or stand unless supported. There was severe ataxia, with loss of position sense in all the extremities; the tendon reflexes were normal; the cutaneous-plantar responses were of flexor type, and superficial sensation was intact. Improvement was gradual.

There can be no doubt that the postoperative ataxia was not the result of damage to the left cerebellar lobe. The postoperative symptoms presented by the patient must have resulted from a lesion of the inferior part of the medulla oblongata, produced in the course of removal of the bulbar angioma. A transverse section of the medulla oblongata at this level showed clearly that the area of insertion of the tumor corresponded exactly with the nuclei of Goll and the internal portions of the columns of Burdach where they enter their nuclei. It is probable, therefore, that an operative injury in this position was the source of the disturbances of sensation which produced the ataxic symptoms.

This syndrome is rare, but cases of similar or related disturbances may be found in the literature. In most instances the lesion was a tumor of the posterior fossa, particularly a hemangioblastoma. Cushing and Bailey (1928) described 2 cases of hemangioma in the region of the midline in which there was definite unilateral astereognosis. Roussy and Levy (1930) reported a case of tumor of the medulla oblongata in which there was so-called cortical dissociation of sensation, particularly astereognosis. This dissociation coincided with integrity of superficial sensation. Lereboullet (1932) and Delay (1935) cited 7 cases of tumor of the fourth ventricle in which astereognosis was present. In most of these cases the tumor lay in the lower portion of the fourth ventricle and exerted pressure on the lower segment of the medulla oblongata. This type of sensory dissociation is even rarer with other lesions of the medulla oblongata, only 2 cases having been reported. The nature of the lesion is unknown. The authors of the 2 cases reported assumed the existence of lesions of the spinothalamic tracts in the medulla oblongata, probably in the internal arcuate fibers between the nuclei and the piniform decussation.

SALL, Philadelphia.

DEVELOPMENT OF SYRINGOBULBIA. F. KRAUSE, Deutsche Ztschr. f. Nervenh. **144**:14, 1937.

Krause has observed 4 cases in which syringobulbia developed on the basis of exogenous factors, such as trauma (2 cases) and infection (2 cases). The clinical and pathologic changes in 1 case of syringobulbia following an infection are reported in detail. A man aged 26 presented symptoms and signs of involvement of the medulla after an attack of "grip." The patient improved and was able to return to work, but was left with some residual symptoms. Three years later, symptoms recurred with greater severity. Irradiation resulted in transient improvement, but the patient became totally incapacitated four years after the onset. He died six years after the onset, after an operation for gastric ulcer. Necropsy showed a cavity in the right side of the medulla, from the posterior longitudinal bundle to the medial side of the olive, extending from the level of the crossing of the pyramids to the upper part of the hypoglossal nucleus. A large cavity was also seen in the cervical and thoracic portions of the spinal cord. The lumbar and sacral portions of the spinal cord were normal. The author concludes that the development of the cavities in this case was due to disease of the blood vessels caused by infection.

MERRITT, Boston.

Experimental Pathology

BERGER'S α RHYTHM IN ORGANIC LESIONS OF THE BRAIN. F. LEMERE, Brain **60**:118, 1937.

It is now generally recognized that the changes in electric potential occurring in the brain at different frequencies may be picked up from the intact scalp and recorded by means of the oscillograph. By far the most outstanding rhythm is that which has a rate of about 10 waves per second—Berger's alpha waves. This rhythm is present in the vast majority of subjects only when they are at rest with the eyes shut. It seems fairly certain that the waves are produced by groups of cells beating in unison in the occipital lobe. As soon as the subject opens his eyes and focuses on an object the occipital cortex is no longer free to beat spontaneously and the rhythm breaks up and disappears.

The present study was undertaken to determine the effect of various cerebral lesions on the alpha rhythm. Electroencephalograms were obtained from 15 normal subjects and from 60 patients with intracranial cerebral lesions. In the normal subjects and in the patients with bilateral generalized cerebral lesions, Berger's alpha rhythm was the same on the two sides.

Unilateral localized lesions of the temporal, frontal or parietal lobes were associated in general with a slightly stronger rhythm on the affected side. Lesions of the basal ganglia resulted in a much stronger alpha rhythm on the affected side, while thalamic and hypothalamic lesions depressed the rhythm on the affected side.

Fairly complete lesions of the occipital lobe on one side resulted in poor or no rhythm on that side. Lesions of the optic radiation, on the other hand, were associated with a strong alpha rhythm on the affected side which was present even with the eyes open, provided the hemianopia was fairly complete.

The findings seem to offer suggestions for further work and already to have been of some value in diagnosis. For example, in cases of hemianopia in which there is doubt as to whether the optic radiations or the occipital lobe itself is involved a strong alpha rhythm suggests the former, while a weak or no rhythm favors the latter localization. In some cases a differential diagnosis of a lesion of the frontal lobe on one side or a cerebellar lesion on the other presents difficulties. A difference between the rhythms on the two sides, especially a slightly better rhythm on the affected side, suggests a lesion of the frontal lobe.

The suggestion of Adrian and Matthews that the alpha rhythm is produced in the cortex of the occipital lobe seems to offer the best basis for interpretation of the effect of these unilateral lesions. Any lesion tending to isolate, but not to involve, the occipital lobe caused strengthening of the rhythm on the affected side. Any lesion, on the other hand, involving the greater part of the occipital lobe produced almost complete absence of rhythm on the affected side. The depressing effect of thalamic lesions on the alpha rhythm on the affected side is less easily understood and requires further investigation.

SALL, Philadelphia.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Presiding*

Regular Meeting, Oct. 20, 1938

THE CEREBROSPINAL FLUID IN CASES OF OPTIC NEURITIS, "TOXIC AMBLYOPIA" AND TUMORS PRODUCING CENTRAL SCOTOMAS. DR. ARTHUR L. WATKINS.

I have studied 120 patients who came to the hospital primarily for loss of vision and were found to have a central scotoma. In all cases one or more lumbar punctures were made. A report of the results of these examinations is the main purport of this paper.

The terminology used in classification of disorders affecting the optic nerves, chiasm and tracts is still confusing. It is necessary, therefore, to make arbitrary definitions. First, all patients with syphilis were excluded. There remained the following conditions: retrobulbar optic neuritis, "toxic amblyopia," optic neuritis and tumors or aneurysms pressing on the optic nerves.

ACUTE RETROBULBAR OPTIC NEURITIS

This group of disorders was characterized by loss of vision within a few hours or days. There was usually tenderness of the eyeballs; the disks were choked, pale or normal, and the visual fields showed central scotomas. There were 40 patients, the average age being 33, with 85 per cent under 40. Visual acuity varied from 20/30 to complete loss of light perception. In 75 per cent of patients only one eye was involved. Although 88 per cent recovered from the acute attack, 18 per cent had recurrences in the same or in the opposite eye. The initial pressure of the cerebrospinal fluid varied from normal to 300 mm. of water. The cell content was normal in 95 per cent; 2 patients showed 19 and 34 lymphocytes, respectively, per cubic millimeter of fluid. The total protein content averaged 34 mg. per hundred cubic centimeters and varied from 19 to 49 mg. Twenty-eight per cent of the 40 patients had an abnormal colloidal gold curve, that is, readings of 3, 4 or 5 plus in the first zone, or rarely in the midzone.

In 27 per cent of all cases the disease was recognized as multiple sclerosis before, coincidentally with or after the visual disturbances. If, however, only the 18 cases are considered in which the patient was followed for more than three years, the incidence rises to 50 per cent. The follow-up study, however, was not sufficient to rule out multiple sclerosis in cases in which the origin was unknown. In 7 of the 9 cases of multiple sclerosis the visual disturbances were unilateral, and in five of these there were strong colloidal gold curves in the first zone. In 3 of the 9 cases of multiple sclerosis, the retrobulbar optic neuritis occurred two, six and fourteen years, respectively, after the first symptoms of the disease; in 3 cases the retrobulbar neuritis preceded the multiple sclerosis by four, three and one year, and in 3 others the retrobulbar neuritis was noted coincidentally with other symptoms.

I conclude therefore, on the basis of examinations in 40 cases of acute retrobulbar neuritis, that the cerebrospinal fluid is normal in this disorder, except when caused by multiple sclerosis. In such cases, which formed from 25 to 50 per cent of the group, the colloidal gold curve sometimes showed a strong reaction in the first zone.

CHRONIC RETROBULBAR OPTIC NEURITIS

In 39 cases the onset of the visual disturbance was slow and gradually progressive over a period of months rather than weeks. The average age was 39, with

62 per cent of patients over 40. Both eyes were affected slightly more frequently than one alone in 54 per cent of cases, and the eyeballs were tender and painful in only 22 per cent. Pallor of the optic disk occurred in 72 per cent, and hyperemia, in 21 per cent; the disks were normal in 7 per cent. There was a central scotoma, and visual impairment progressed to nearly complete blindness. Lumbar punctures revealed no abnormality in the initial pressure, cell content, total protein or colloidal gold curve. The total protein content averaged 35 mg., the upper and lower limits being 49 and 15 mg., respectively, per hundred cubic centimeters.

The cause was unknown in 85 per cent of the cases; multiple sclerosis was present in 15 per cent. Because of uncertainty in diagnosis, exploratory operation was performed in 2 cases in this series; in neither were gross pathologic changes revealed in the optic nerves, chiasm or sheaths. Although no pathologic material is available, the presence of tumors in this group is unlikely, as the patients were followed for from three to twenty years without the observation of roentgenologic changes or the development of other symptoms or signs. In no case was there any improvement in vision in spite of various treatments, including general hygienic measures, spinal fluid drainage, search for and eradication of foci of infection, if present, and fever therapy with typhoid vaccine. In some of the cases the condition might have been classified as Leber's disease, but because of uncertain hereditary background the diagnosis was not made.

TOXIC AMBLYOPIA

This condition was diagnosed in 30 cases. The average age was 52. There was slowly progressive loss of vision in both eyes, although not necessarily to the same degree. An exception was a case of acute lead intoxication in which the onset occurred within twenty-four hours. The eyeballs were not tender in any instance; the optic disks were either normal or slightly pale. The diagnosis was usually made from the presence of a cecocentral scotoma, particularly for red and green; in some cases it was made from a history of indulgence in alcohol and tobacco and the presence of a central scotoma similar to that in retrobulbar neuritis. The initial pressures of the cerebrospinal fluid were usually from 80 to 210 mm. of water. In general there was no pleocytosis, although in 1 case there were 13 lymphocytes. The total protein averaged 33 mg. per hundred cubic centimeters, being distinctly abnormal in only 2 cases, with the highest reading 70 mg. The colloidal gold curve was normal in all cases.

In summary, a normal cerebrospinal fluid was found in over 90 per cent of cases of toxic amblyopia.

OTHER TYPES OF OPTIC NEURITIS

This group includes cases in which there was diminution of vision, papillitis or constriction of the field of vision. The classification is used here arbitrarily. It is possible that in these cases relative central scotomas were present though not demonstrated. The relation to cases of retrobulbar neuritis is close. The two groups are separated only because the fields of vision differed and loss of visual acuity was less marked. In the 5 cases included the ages of the patients ranged from 4 to 46 years. There was tenderness of the eyeball in only 1 instance. There was slight choking of the disks and peripheral constriction of the visual fields; in one-half the cases involvement was only unilateral. Lumbar punctures revealed normal initial pressures, from no to 10 lymphocytes, normal total protein and normal colloidal gold curves. In all cases the condition developed rapidly during a few days, and normal vision was regained. In 2 cases pansinusitis occurred coincidentally, and in another, hay fever. One patient had definite lead intoxication, which seemed to be of etiologic significance.

In 6 other cases optic neuritis was present but was not the chief complaint. In 3 there were transverse lesions of the spinal cord with retrobulbar neuritis, which was thought to be due to an unclassified infection but which fitted into the clinical

syndrome of neuromyelitis optica. In the other 3 cases there was blindness with central scotomas and multiple peripheral neuritis. Autopsy in 1 of these revealed extensive periarteritis. In the 3 cases of neuromyelitis optica and the 2 of multiple peripheral neuritis with optic neuritis there was definite abnormality of the cerebrospinal fluid; from 10 to 30 lymphocytes, and a total protein content as high as 585 mg. per hundred cubic centimeters. In the case of periarteritis the fluid was normal.

TUMORS

Eleven patients came to the hospital primarily for loss of vision, without other appreciable symptoms. At operation or autopsy tumors were observed to be pressing on the optic nerves, chiasm or tracts. At first a diagnosis of retrobulbar neuritis or toxic amblyopia was made. In 8 cases definite central scotomas were found, and in 3 loss of vision was so extensive that accurate determinations of visual fields were impossible. The optic disks showed atrophy in 7 cases and choking in 1; in the other cases they were normal. In no instance were the eyeballs tender or painful on motion. Visual loss was bilateral in 9 of the 11 cases. In 5 cases stereoscopic roentgenograms of the skull, without injection of air, suggested tumor in the region of the sella turcica; in the other 6 they were reported as normal.

The initial pressures of the cerebrospinal fluid were normal in 7 cases and slightly elevated, above 200 mm. of water, in the rest. The cell content was normal in all but 1 case, in which there were 50 lymphocytes. The total protein averaged 101 mg., being greater than 50 mg. in all cases. The colloidal gold curves showed a mild midzone reaction in 2 cases and was normal in the others. The elevated protein content was of clinical value in leading to a correct diagnosis and operation except in a case of aneurysm, in which the diagnosis was not made until autopsy. The pathologic reports in these cases were: pituitary tumor, in 3; meningioma, in 7, and aneurysm of the circle of Willis in 1; in all cases the tumor caused pressure on the optic nerves. In 11 cases serving as controls, in all of which there were similar histories and complaints only of visual loss, a diagnosis of retrobulbar neuritis was first entertained, but bitemporal or homonymous hemianopa was discovered. Of 8 cases of bitemporal field defect, the optic disks were normal in 5 and atrophied in 3; in 1 case there were atrophy in one eye and choking in the other. In 3 cases of homonymous hemianopia there was primary atrophy of the optic nerve. Roentgenograms of the skull were normal in 4 of these 11 cases and showed evidence of tumor in the pituitary region in the others. The initial spinal fluid pressure was normal in 10 cases and elevated in 1. Cell counts were normal in all but 1, in which there were 21 lymphocytes. The colloidal gold curves were also normal. The total protein content averaged 60 mg. per hundred cubic centimeters, but was normal in 4 cases. The pathologic observations at operation or autopsy included meningioma, pituitary tumor, craniopharyngioma and aneurysm, all of which pressed on the optic chiasm.

The conclusion is drawn from the 22 cases of tumor that the cerebrospinal fluid pressure, cell content and colloidal gold curve may all be within normal limits, but that the total protein is usually increased from two to five times the normal when there is present a central scotoma from pressure of tumor or aneurysm on the optic nerves or chiasm.

Comment.—A review of the literature reveals 402 cases of retrobulbar neuritis, in 160, or 40 per cent, of which multiple sclerosis was present. Sinal infection was sought in each of my cases and was found only once. In about one half of my cases no satisfactory etiologic agent was determined. Clinically, the important point in diagnosis is the mode of onset and course. Acute conditions nearly all improve spontaneously before the diagnosis of tumor need be seriously entertained. They occur at an early age, are largely unilateral and are associated with tender, painful eyeballs. Chronic retrobulbar neuritis offers difficulty in differentiation from tumor, as the course of the two conditions is not dissimilar and prognosis for spontaneous recovery is poor. It is in this group particularly that examination of the spinal fluid may be of value.

The diagnosis of toxic amblyopia is usually not difficult. The condition occurs in a distinct older age group; characteristic field defects are present, and in general the cerebrospinal fluid is normal, although there may be some abnormality. In 90 per cent of my cases the spinal fluid was normal; clinically, increase of total protein was a distinct factor in changing the diagnosis from toxic amblyopia to tumor and in subsequent operative improvement.

In the small group of cases in which the disease was classified as optic neuritis there was little difficulty in differentiation from tumor, as the course was benign with fairly rapid recovery and other etiologic factors were usually apparent. Normal pressures helped to differentiate the condition from papilledema.

The cases of tumor are of particular interest. Bitemporal or homonymous field defects were of the most diagnostic value and led one to suspect tumor; roentgenograms often bore out this assumption. In a certain number of cases the fields may be similar to those of retrobulbar neuritis of other origin, as noted by Kennedy; it is these cases in which the protein content of the spinal fluid may be of differential significance.

Chiasmal arachnoiditis has been mentioned as a cause of blindness and is said to produce various defects in the visual fields. In no case in this series was the diagnosis of this condition confirmed.

SUMMARY AND CONCLUSIONS

1. In patients with acute retrobulbar neuritis without demonstrable cause the spinal fluid was normal except in older persons with associated multiple sclerosis (25 to 50 per cent). In these cases there were a few lymphocytes, a high normal total protein content and a strong colloidal gold reaction in the first zone.

2. The spinal fluid was normal in 95 per cent of patients with so-called chronic retrobulbar neuritis and probable "toxic amblyopia."

3. In each of 11 patients with a tumor or aneurysm producing central scotomas, the spinal fluid protein was increased by from two to five times the normal amount. This abnormality of the spinal fluid was a valuable diagnostic point in differentiating tumor from other causes of central scotoma.

DISCUSSION

DR. JAMES B. AYER: I have studied this material with Dr. Watkins. His analysis is probably correct within a small percentage of error. I am not so sure that the title of the paper is correct. Retrobulbar neuritis is a term which is used in different ways by different authors. I think the title should be "Central Scotoma: Acute and Chronic."

For years, in collaboration with Dr. George Derby, I made lumbar punctures. We found the fluids normal and I lost interest. When Dr. Watkins observed cases of tumor in which there was a high protein content I became interested. He reviewed a large number of cases and found that retrobulbar optic neuritis resulting from a toxic or inflammatory state or from multiple sclerosis is different from that caused by tumors. This is the essential point of the paper. I think Dr. Watkins deserves credit for placing these groups together.

DR. MADELAINE BROWN: Many believe that retrobulbar neuritis is the first symptom of multiple sclerosis. Dr. Putnam and I have been analyzing the records in cases of multiple sclerosis at the neurological unit of the Boston City Hospital for the past seven or eight years, with special interest in the first symptom. Acute retrobulbar neuritis was not a common first symptom in the patients with this disease. Of 95 records analyzed, only 3 mentioned acute retrobulbar neuritis as a first symptom. One must judge largely by the patient's story; a much better, though more difficult, method is that of following patients with conditions diagnosed as retrobulbar neuritis. As to the literature on such observations of patients with retrobulbar neuritis and the later development of multiple sclerosis, I have found only 3 references, 2 in the German and 1 in the English. The first German article was by Fleischer, in 1908, who followed 31 patients with preexisting acute

retrobulbar neuritis. His first patient had had retrobulbar neuritis in 1877. Of the 31 patients, he found that multiple sclerosis developed in 11. In the other German paper the percentage was slightly smaller. Heckford, of London, followed 10 patients with acute retrobulbar neuritis; in none of them did multiple sclerosis develop. If one has acute retrobulbar neuritis, then, one's chances are from 0 to 35 per cent of having multiple sclerosis later.

DR. H. HOUSTON MERRITT: The significant point that Dr. Watkins has made is that when there is a high protein content of the cerebrospinal fluid in a patient with symptoms of retrobulbar neuritis, the underlying cause is a tumor. I wish to ask a few questions. Of the patients with acute retrobulbar neuritis and an abnormal gold curve, were there any without multiple sclerosis? Were there any patients in whom multiple sclerosis developed who showed a normal gold curve? In other words, can the spinal fluid in the acute stages indicate whether or not the patient will have multiple sclerosis?

DR. TRACY J. PUTNAM: I have found that central scotoma is not infrequent with tumors in the region of the chiasm, but one seldom sees a scotoma which is not accompanied by temporal defects on one side or the other. If this was true in any of the cases described by Dr. Watkins, he would do a great service in reporting in detail the precise findings. On the other hand, neuritis may produce bitemporal defects, as has been shown by Roenne. There are few pathologic studies on retrobulbar neuritis. Roenne studied cases of central scotoma associated with diabetes and with alcohol and tobacco intoxication. He observed plaquelike demyelination with gliosis. In the only other case adequately described, that of Birch-Hirschfeld, the condition accompanied carcinoma of the ethmoid sinus with suppuration. In this case a thrombosed vein extended from the sinus into the optic nerve.

It is hard to make a differential diagnosis between multiple sclerosis and retrobulbar neuritis. I wonder if it is Dr. Watkins' belief that a complete separation can be made between cases of acute retrobulbar neuritis and those of local multiple sclerosis.

DR. A. L. WATKINS: In answer to Dr. Merritt's questions: The colloidal gold curve was abnormal in some cases in which multiple sclerosis did not develop during the time I studied them. There were 2 cases of neuritis with multiple sclerosis in which changes in the gold curve were not shown.

In answer to Dr. Putnam: There were many more cases of tumor in which there first appeared a central scotoma and later bitemporal defects. This finding is of great value in differentiating cases of tumor from those of retrobulbar neuritis. In other cases there was no impairment of temporal fields. Protein was the only feature of definite value in differentiating the two conditions.

Another point of interest is that of tenderness. There was no tenderness of the eyeball in cases of tumor. There was almost always tenderness in cases of retrobulbar neuritis.

THERAPEUTIC USE OF CURARE AND ERYTHROIDINE HYDROCHLORIDE FOR SPASTIC AND DYSTONIC STATES. MICHAEL S. BURMAN, New York.

This article appears in full in this issue of the ARCHIVES, page 307.

NEW YORK NEUROLOGICAL SOCIETY

CHARLES A. MCKENDREE, M.D., *President, in the Chair*

Regular Meeting, Oct. 4, 1938

PRESIDENTIAL ADDRESS: TRADITION, TRAINING AND GOALS. DR. CHARLES A. MCKENDREE.

JACKSONIAN SEIZURES OF REFLEX ORIGIN: REPORT OF A CASE. DR. HANS STRAUSS (by invitation).

A woman aged 34 suffered from the sequelae of cerebral damage in early childhood resulting from hemorrhage or meningoencephalitis. An encephalogram showed dilatation of the left lateral ventricle and marked increase in filling with air at the surface of the left central and parietal regions. As a consequence of the cerebral lesion the patient had suffered since childhood from slight right spastic hemiparesis with hypesthesia for all qualities and from jacksonian seizures on the right side. These convulsions were partly spontaneous and partly reflex, resulting from various stimuli on the right side of the body and the sense organs. The reflex convulsions and their provocation by stimuli applied to the skin and the mucous membranes of the right side, by voluntary movements on the right side and by acoustic stimuli were demonstrated by motion pictures. Acoustic stimuli provoked convulsions when applied to either ear, but they were much more effective when presented to the right ear. Optic stimuli, too, provoked convulsive symptoms. Flashing light into either eye usually had a more convulsive effect when the light was projected to a part of the retina corresponding to the right visual field than when it was projected to a part corresponding to the left visual field. Stimulation of the right eye with diffuse light produced convulsive symptoms of more severe character and after a shorter time than stimulation of the left eye. When a certain amount of light was presented to one eye only the convulsive effect was much more pronounced than when the same amount of light was presented simultaneously to the other eye. This observation shows that more stimulation does not necessarily mean more pronounced convulsive effect and that the convulsive effect may even be reduced by the simultaneous application of another stimulus.

Analysis of the effect of voluntary movements had the following results: Passive imitation and reproduction of an effective voluntary movement by electric stimulation were ineffective. The voluntary movements which started convulsions when performed as isolated movements during the experiments did not cause any twitching when performed as part of an action of daily life. This indicates that the central mechanisms underlying these psychologically different performances of movements, which are identical in their coarse external appearance, must differ from one another. When an isolated movement had been used over a long period to produce seizures it became ineffective, and new movements had to be used to produce an attack. At the same time, when the movement became ineffective it was obvious that the patient had learned to make it without paying much attention to it. This shows that there must be a difference in the physiologic mechanisms concerned with the performance of a learned movement and those concerned with the performance of a new, unaccustomed movement.

When a solution of cocaine was applied to the right conjunctival sac it was impossible to provoke convulsions by any stimulus. This means that elimination of stimuli from one point had an influence on the effect of stimuli from many other points. After several applications of cocaine not only the convulsive excitability disappeared for the period of anesthesia but a permanent decrease of excitability resulted. After repeated applications of cocaine within four months it became impossible to induce reflex convulsions by any means. This shows that temporary elimination of stimuli may have a permanent effect.

DISCUSSION

DR. S. BERNARD WORTIS: Dr. Strauss has reported an important case and has studied it in a comprehensive manner. It is difficult to explain, or to understand exactly, most of the phenomena that Dr. Strauss has described. The total stimuli which come to an organism are productive of convulsive seizures, particularly in persons addicted to seizures. The phenomenon of a convulsion has been aptly described as comparable with an overflow from a spring which is fed by many subterranean sources. The subterranean sources that feed this spring

and overflow in a convulsion may be focal lesions of the brain, psychogenic factors, occlusion of the blood supply to the brain, accumulation of toxic substances which circulate and impair the metabolism of the brain and hereditary factors (i. e., the tendency of the brain to be more than normally vulnerable to noxious stimuli). Scars can undoubtedly produce convulsogenic stimulation when they occur in the brain. The work that has been done on strychninization of the cortex of animals proves that one can produce convulsive seizures when impulses are directed through such areas, thus demonstrating that the velocity of impulses as they pass through the brain is a factor which can produce or facilitate seizures. Undoubtedly, scars produce similar shunting of impulses.

This raises the question of the total quantity of sensory impulses (i. e., stimulation) which comes into the central nervous system over the fifth cranial nerve. It is pertinent that the sensory part of the trigeminal nerve is represented as a large bundle of fibers—the trigeminal lemniscus. This must represent a large sensory inflow from the head area of the organism; it was a factor sufficiently great in Dr. Strauss's case to precipitate a seizure. When this large sensory inflow was partly reduced by cocainization of a peripheral end organ, reflex convulsive seizures were stopped. At this point, it is worth mentioning work by Soma Weiss, in which he cocainized local areas of the skin to prevent the occurrence of large areas of pain referred from deep viscera. Weiss's work pertained to cardiac disease particularly; it perhaps indicates the direction for interest in local anesthetization of focal epileptogenous zones, when these are clearly defined in the aura of the epileptic attack. I think that Dr. Strauss's paper emphasized this important factor. In many cases, even in the presence of focal lesions of the brain, one may find that local peripheral anesthetization of the skin helps to reduce the total inflow of stimuli and prevent the occurrence of reflexly stimulable convulsive seizures.

Dr. Robert W. Laidlaw: I am interested in Dr. Strauss's presentation because of a somewhat similar case that is being studied at present in the division of child neurology at the Neurological Institute. The patient is a boy aged 7 who for the past two or three years has had typical jacksonian attacks on the right side brought about by stimulation of the right ear. They frequently come when the mother is washing the ear. In a boy aged 7 this may at first suggest the possibility of a psychogenic basis; however, that phase has been studied thoroughly, and my colleagues and I believe the child to be well adjusted. It is also pertinent that after one of the attacks there is a period of at least three or four hours during which any degree of stimulation of the right ear fails to produce a recurrence. The attacks begin, much as was the case with the patient of Dr. Strauss, with twitching of the right side of the face, which spreads to the shoulder. The right arm then undergoes clonic movements, and the right leg is extended. Neurologic examination between attacks revealed entirely normal signs, but immediately after a seizure there are hyperreflexia on the right and muscular weakness. A pneumoencephalogram was normal. The boy is able to bring on an attack by rubbing his right ear, and he is a good witness; he says that there is a well defined area in the posterior portion of the ear which is the "trigger zone." Stimulation of other parts of the ear has no effect. When he tries to bring on an attack he can tell about two minutes before the seizure starts whether he will be successful. Sometimes he rubs the ear and nothing happens. At other times he says: "I feel it coming." When asked to describe the feeling, he says: "It is something like a feeling of tightness in the head." The attack starts in the face and passes to the arm and then to the leg. As I said, study of the case is still incomplete.

Dr. Richard M. Brickner: I wish to express my appreciation of this excellent case study and of Dr. Strauss's presentation of it. One feature is incomprehensible to me, if one looks on the condition as strictly organic. I do not mean that there is no lesion; of course, there is. I am not one readily to make a diagnosis of hysteria, especially when there is an organic lesion of the brain.

In the auditory and optic experiments, it was evident that there was equal stimulation of the two sides of the brain. Dr. Strauss's explanation of the optic part of the experiment is not altogether satisfying. I think that the same explanation would hold for one eye as for the other. With regard to the auditory part, although it has long been known that each ear is represented in both hemispheres, in recent years there has been an opportunity to learn that the representation is equal on the two sides. There have been 5 cases of complete right hemispherectomy in which hearing, tested with the audiometer, was equal on the two sides. This tends to show that when hearing was stimulated in Dr. Strauss's patient both sides of the cortex were aroused. I wonder whether this is not part of the picture which one must call hysterical, even though one does not wish to do so.

The visual and auditory parts of the experiment are perhaps similar to what is seen in truly hysterical patients with hemianesthesia, in whom vibratory sense on the side of the sternum corresponding to the anesthetic side of the body is often not perceived. Is it not possible that in these auditory and visual tests one is seeing the counterpart of the same thing?

DR. PAUL SCHILDER: Has Dr. Strauss tried to provoke the seizures in his patient by a. suggestion of the sensory stimulus? That would be an interesting extension of the examination. A second question, which also belongs in this category and would perhaps be of theoretic interest, is whether one can produce the attacks not only by unconditioned but by conditioned stimuli. I think that experiments of this type might lead deeper into the mechanism of such seizures.

I should not say that conditions of this type are to be considered as hysteria or as disturbances with hysterical components. However, in all organic disorders there are phenomena which are best classified as pattern formations, and in them personality trends are always present. It is such a pattern formation when the patient reacts only to a stimulus from the affected side. The question which Dr. Brickner asked concerning hearing must be considered in relation to vision, since stimulation of the right eye had a different effect from that of the left, in spite of the bilateral representation of the visual field in the optic region. This is indeed a reaction similar to that in hysteria. This does not mean that the case is one of hysteria, but it shows that the pattern formations in organic and in psychogenic conditions in many instances may be identical, a conclusion to which one is forced more and more as one compares organic and psychogenic disorders.

DR. L. A. SALMON: If one could produce stimulation in this case without the patient's realizing to which side of the body the stimulus is being applied the results might be interesting. A procedure which would be worth trying is the Japanese fan maneuver. I should perform it rapidly and note whether the convulsions could be produced.

DR. HANS STRAUSS: In answer to the questions concerning the psychic state of the patient, I should say that she is feebleminded. She has never shown any signs of pronounced suggestibility, and I do not think that production of the convulsions and the effect of cocaine can be explained as a result of suggestion. The application of homatropine or saline solution to the right conjunctival sac had no effect on the convulsions. I intended to perform the experiments in hypnosis proposed by Dr. Schilder, but neither I nor any one else has succeeded in hypnotizing the patient. Many other experiments which had been planned could not be performed as it finally became impossible to provoke reflex convulsions by any means. I previously pointed out that the greater effect of stimulation of the right eye and ear than of the left can be explained by the closer anatomic relations of these organs with the left hemisphere.

The treatment of epileptic attacks by cocainization of the locus of the aura has been performed successfully by Mondio (*Riv. di pat. nerv.* **39**:156, 1932). Analysis of the electroencephalogram allows exact determination of the cerebral

focus of the attack. Therefore, it might be possible in some cases to stop the convulsive disorder by cocainization of the peripheral representations corresponding to the cerebral focus.

MISCONCEPTIONS OF LEGAL INSANITY. DR. GREGORY ZILBOORG.

The expression "legal insanity" is today a household term of the legal and medical profession; it is accepted as denoting a specific condition, the existence of which is not questioned and the meaning of which is taken for granted. Seldom, if ever does one ask oneself what its scientific implications are, and, as far as I know, no one has succeeded in defining its clinical meaning.

In this connection it is both injudicious and disingenuous to overlook the fact that the concept of legal insanity is a product and tradition of the judiciary, and not of medicine (psychiatry). The average man, who is the carrier of common sense morality, disapproves of murder, but tends to excuse the person who is "out of his head" or "does not know what he is doing." Common law is this moral sense crystallized in the form of established tradition, while the penal code is the statutory expression of this tradition. The concept was arrived at by generations of ethically minded and morally inspired good citizens (some of them were physicians) and the judiciary, not by scientific medicine. History shows that the jurist borrowed psychiatric concepts, utilized psychiatric terminology and converted them into his own concepts of legal insanity. In the light of this development there is nothing offensive to the law or to the psychiatrist if, in the discharge of his medical (and this includes his medicolegal) duties, the psychiatrist uses his moral and scientific right to subject the psychiatric excursions of the law to scientific scrutiny.

Unfortunately, the problem cannot be simplified by divorcement of the law from psychiatry or of psychiatry from the law. Such a step would only create a medicolegal "no man's land," which would serve to enhance the confusion.

About one hundred years ago, in 1843, a group of English judges was asked by the lords to answer a series of questions regarding legal insanity in the case of McNaghten, which had been judicially closed. Relying on the tradition which was deeply rooted in the past and using the meager psychiatric knowledge of the time, the judges rendered an opinion which read in part as follows: "We have to submit our opinion to be that the jury ought to be told in all cases that every man is to be presumed sane, and to possess a sufficient degree of reason to be responsible for his crimes, until the contrary be proved to their satisfaction; and that, to establish a defense on the ground of insanity it must be clearly proved that, at the time of committing the act, the party accused was laboring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing, or if he did know it that he did not know he was doing what was wrong."

As it stands today, the law in all the states (except for New Hampshire) follows substantially, and at times textually, the same formulation.

There is more often than not an ideologic struggle between psychiatry and the law. The law perennially accuses the psychiatrist of being a poor jurist, and psychiatry reproaches the jurist for not being a good psychiatrist. On both sides there is a deep feeling that a moral principle is being grossly violated, and the emotional undertone of this antagonism has tended to interfere with the objective examination of fact.

This emotional discussion has been going on literally for ages. In 1838, Isaac Ray, one of the founders of what is today the American Psychiatric Association, wrote with dignified scorn on the "blind obstinacy" of the law, and in the seventeenth century Lord Hale revealed a no less derogatory attitude toward medicine. During the Renaissance, Weyer, the founder of modern psychiatry, was contemptuously branded by the Saxon lawmakers with the label "medicus," and farther back in the fifteenth century the "Malleus maleficarum," a famous textbook

of the Inquisition, defined the limits of the medical man's competence, restricting him to the diagnosis and treatment of purely "natural" (organic) phenomena.

Today, the layman, the law courts and even the testifying psychiatrist continue to reflect this respect for the importance of grossly organic factors, often holding them as the basis for medicolegal conclusions in cases in which a plea of insanity is interposed. The megalomanic conviction that man is full master of his own fate, that the will is free, continues unchanged except in advanced quarters of psychiatry. An outstanding example is the case of the 65 year old Albert Fish, executed by the state of New York for the murder of the 9 year old Grace Budd. He butchered the child, with the fantasy or in the hope of eating her, and in his paranoid rapture was happy that she died an innocent child, a virgin. A physician who testified for the state reported that the man was rational, that his preferred method of masturbation, the insertion of needles in the perineum, was a case of "just bad sex habits" and that the defendant's coprophilic habits were not indicative of insanity.

The medical man, as well as the jurist, has in many cases accepted a dual standard; he has acknowledged the existence of two insanities—legal and medical. Such straddling is as scientific as to say that a given person has tuberculosis medically but not legally. The same is true of so-called partial insanity. There is nothing partial about a human being, whether he suffers from pneumonia or schizophrenia.

Human instincts cannot be abolished, and the law stands firm on the demand that they be socialized. In this respect the law and psychiatry have a common ideal; it is the means of achieving the ideal that causes the antagonism. Weyer sought to reconcile the two points of view when he undertook the task of freeing patients from unreasonable prosecution. He accepted the classifications and tests provided by the law and applied them in his cases in a strictly empiric and objective manner, but in the light of purely medical knowledge. He came to striking and assertive conclusions.

One cannot change the law quickly and must submit to it as a fact stronger than the physician. It is a right of the physician to stand firmly by only that which he is competent and qualified to know—his clinical knowledge, which has been accumulating during the most fruitful years of scientific development. Official psychiatry would perform the greatest service to law and medicine if it would decree that any expert psychiatric testimony admitting the existence of legal insanity and accepting the concept of legal responsibility is not in accordance with the basic scientific tradition of the profession, is not in accordance with clinical facts and automatically and officially disqualifies the expert in the eyes of the medical profession.

The crux of the question lies in the word "know"—did the defendant "know" the nature and quality of the act, and if he did, did he "know" that it was wrong? The law automatically assumes that the knowledge of a child differs from that of an adult with reference to the responsibility in the commission of a felony. Psychiatry recognizes the difference between knowledge divorced from affect and knowledge so fused with affect that it becomes a human reality. It is doubtful whether an enlightened judge would be able to oppose a psychiatric concept of knowledge if the psychiatrist insisted that he has no other concept, that he cannot take the word "know" for granted any more than he can assume that a lawyer's psychiatry is clinical psychiatry. The psychiatrist, instead of leaving his clinical armamentarium at the entrance door of the court and borrowing whatever antiquated speculations are offered him by battling lawyers, will feel on more solid ground, and will become more effective, if he carries his strict clinical standard directly to the witness stand.

DISCUSSION

DR. SMITH ELY JELLIFFE: To my colleague Dr. Zilboorg I am indebted for a copy of his paper and for the privilege of saying a few words about the theme brought to the consideration of this meeting.

It is a thorny problem this, both for medicine and for the law—so thorny that I am reminded of the ditty:

"There was a man in our town
And he was wondrous wise
He jumped into a bramble bush
And scratched out both his eyes.

And when he found his eyes were out,
With all his might and main
He jumped into another bush
And scratched them in again."

I wonder if many could manage as well between the bramble bushes of so-called medical and legal insanity? Dr. Zilboorg has clearly shown how brambly the two bushes are, and for me "not half has ever been told."

With many another, particularly with my friend Dr. White, I have in season and out of season held that it might be possible to save some eyesight if, first, one removed the term "insanity" entirely from medicine and relegated it *in toto* to the legal bramble patch, if the lawyers want it. Insanity, as a term, should function solely as a legal concept. It is an abstraction, which for physicians has no factual meaning. Physicians are interested in human beings and their difficulties, their diseases if you will—the particular bramble patch under consideration being mental disease. They look at factual happenings—individual psychotic, psychoneurotic, psychopathic and criminal activities, not a generalized legal concept dealing with personal or property rights, important as that is in its own frame of reference.

Dr. Zilboorg asked you to look back to the Middle Ages. I shall ask you to look back further, to the beginnings of this trouble. Being away from my library, I do not wish to be pinned down to any references; but I think this business started with the Romans in the heyday of their property stealing; it was a product of their particular type of thinking, so different from that of the Greeks. The Romans became property minded and impatient with analytic mental processes. They undoubtedly met the same situations concerning murder, theft, forgery, contract making and will making that exist today, and they knew that in certain persons something was wrong in the "upper story." One writer stated that they said, in essence: "Away with your Greek subtleties, your anosias, paranoias, amentias. We do not know what they mean. Let us lump the lot of them and call them 'insania.'" And thus there arose the fiction of a disease called insanity, still anachronistically retained by lawyers as a valid expression for a mental disease. It has no such value, even if the tyranny of a word for two thousand years still "scratches one's eyes out." The term insanity should be relegated to the legal bramble bush. It is a concept of a legal status. It is not a medical concept. A court of law alone can determine whether a person should be adjudicated to be "insane."

The physician's bramble bush is of another order. He is interested in the factual behavior of the person who, in the committing of an antisocial act, may be sick, who has a mental disorder or defect.

Now where is the rub? It enters when one needs to step from one category into the other and, more particularly so far as the physician is concerned, to say how sick the man is and from what kind of sickness he suffers, because, and here is the important point, society—as represented by the law—must needs know if the sickness under consideration makes it incumbent that society, again through

its legal masks, shall deal with the individual man in a special or specific manner, for its or the person's best interests.

Dr. Zilboorg has wisely limited his discussion to one or a few issues, to homicide especially. However, there are a number of issues, all varying somewhat as to their definition in the forty-eight states of the Union and, moreover, with each pronouncement of a judge of certain rank, constantly undergoing modification, contradiction, confusion or clarification.

For the verdict of homicide in the state of New York and in most other states, as has been pointed out, a person, kindly note my phrasing, should be declared, not be, "insane" and should not be held accountable for his act if "by reason of mental defect or disease he did not know the nature and the quality of his act, and did not know that it was wrong." Dr. Zilboorg has traced the lineage, in part, of this definition of right and wrong and of knowledge of the act. It is not a test; it is a definition and, as is known, varies in different jurisdictions. Thus, in New Jersey there is added to the definition the "ability to control an impulse." Persons with compulsion neuroses should do their killings in New Jersey.

I shall not attempt to expand further on the metaphysical absurdities and gross logical inadequacies of these many definitions or on the extreme difficulties and impediments to gathering exact information that the legal procedures have elaborated through the years. Dr. White, in his excellent little book entitled "Insanity and the Criminal Law," has done it better than I could hope to do, even if there were time to epitomize his lucid statements.

Dr. Winfred Overholser, Washington, D. C. (by invitation): It is always a pleasure to discuss one of Dr. Zilboorg's papers. He has presented a combination of philosophy and realistic dealing with a problem which is much in the minds of the public.

Dr. Jelliffe has discussed at least one point which I should have amplified if he had not, that is, we, as physicians, should not speak of "insanity." In other words, "medical insanity" is a contradiction in terms and is a phrase which should not be used at all by medical men. Furthermore, when one speaks of legal insanity one is not talking about a unit. In law the word "insanity" means many things, even though a great many persons have the notion that it refers to something definite. It all depends on what the "universe of discourse" is. Insanity, as far as criminal law is concerned, differs from insanity as regards commitment to a hospital for mental disease. It is much different from insanity so far as it concerns the annulment of a marriage or the execution of a valid will; in other words, the law itself has no single standard or test or definition of insanity. In many states, the tradition of the McNaghten case has been handed down through the decisions of the courts. So far as I know, there are not more than five states that are unfortunate enough to have the test embalmed in the statutes in the way it is in New York; I say unfortunate because once the test becomes embedded in the laws one is almost bound to have more difficulty in changing it than if it is left to the enlightenment of the judges as they interpret the law. Some courts have come far from clarifying the McNaghten rules. They have, indeed, sometimes added to the confusion; they have garbled and taken snatches of other decisions here and there; some of the decisions which have been laid down make amusing, and in other cases painful, reading. It has not always been that the judges, retrospective though they may be, have failed to change that outlook. I am often reminded of an incident which occurred when I called on an old judge sitting in one of the courts of Massachusetts. He was trying a case which under the Massachusetts law rejoiced in the poetic name of bastardy, and the question of the period of gestation was the point at issue. He was preparing to charge the jury, apparently, and I noticed the book which he was consulting. It was a legal dictionary, which quoted as authority on this obstetric question the statement by Lord Coke, and that antedated by a long time even the McNaghten case! In spite of their retrospectiveness, however, judges have been willing at times to bow to the progress of psychiatric knowledge. The supreme court of New Hampshire

did a progressive thing as far back as 1869 in throwing over the so-called McNaghten rules and saying that they had been erroneously promulgated as matters of law, that the question of mental disease was one of fact and should be left to the jury, without attempt to set up any hard and fast rules.

There is one point in the McNaghten opinion that I may mention as having been generally overlooked, even by a great many judges today. McNaghten was a paranoid person. The questions that were put to the judges in England, although they were hypothetic, clearly had to do with McNaghten. The judges said that these tests, these instructions, these so-called rules or definitions, should be "accompanied [in the judge's charge] with such observations as the circumstances of each particular case may require." If judges would bear that caution in mind, the jury might be less in a fog on matters having to do with "responsibility."

In connection with some of the remarks by Dr. Zilboorg, a comment of the supreme court of New Hampshire in the case of State vs. Pike (49 N. H. 399), previously mentioned, is interesting. "Legal tribunals have claimed these tests as immutable principles of law, and have fancied they were abundantly vindicated by a sweeping denunciation of medical theories—unconscious that this aggressive defense was an irresistible assault upon their own position." I think this summarizes effectively the unconscious motives of some of the courts in their diatribes against psychiatry.

In the July 1938 issue of the *American Journal of Psychiatry* (page 219) was the report of a lunacy commission of New York state in a case which has not yet come to trial; for that reason I shall not name the defendant. It is an excellent example of what Dr. Zilboorg referred to, namely, psychiatrists trying to speak the language of jurists. In that report a categorical opinion as to the legal "responsibility" of the defendant is given, although he did not talk to the commission. There was no psychiatric examination, certainly, not such as is made in hospitals for mental disease. It is a painful thought that the defendant was not even committed to a hospital where he could have been properly observed, as requested by his counsel, and where a psychiatric opinion could have been given; I am sure all will agree that a jail is hardly a favorable milieu in which to examine a defendant!

It is not true that the courts and the legal profession in general have been blind to the fact that there are difficulties or that there are instances in which the courts are not acting wisely. At a meeting of the New York Academy of Medicine, about 1929, Justice Cardozo gave an enlightening address on the relation between law and medicine; it is found in his charming volume entitled "Law and Literature." Today, the American Bar Association is much interested in the problem of bringing psychiatry closer to the law. There are ways, perhaps, in which it can be done; the situation is not entirely hopeless. It is extremely important, however, that the medical profession stick to its last and not attempt to go over into the field of law, for there is plenty that medicine can do without trying to speak a language which it can do only lispingly. Ultimately, further thought, and perhaps even action, will be given to a possible solution—a solution which was attempted as far back as 1910 in the state of Washington, where they tried to throw out from the trial all consideration of the mental state of the defendant, reserving the matter of the mental state for the disposition which would come after the guilt or innocence of the defendant had been determined. Unfortunately, that law was declared unconstitutional, as were similar laws, such as those tried in Mississippi; however, with the increasing tendency to make the matter of disposition less mandatory, to give the courts greater discretion in disposition, there will be less bickering in the courtroom before the jury over a metaphysical question which has little to do with psychiatry.

DR. KARL M. BOWMAN: Dr. Zilboorg has given an excellent presentation of some difficulties surrounding the problem of legal insanity. All agree that the present situation is unsatisfactory. The question is what can be done to improve the situation.

I wish to point out that the problem of legal insanity practically never arises except with regard to serious crimes, such as murder or rape. If a person is arrested on a charge of vagrancy and is found to be suffering from a mental disorder, no one questions but that he should be committed to a hospital for mental disease. No one raises the question of legal insanity and demands to know whether the patient realized the nature and quality of his act or knew the difference between right and wrong. Every one agrees that he is mentally sick and that he should therefore be placed in a hospital for such patients. If, however, the person has committed a serious crime the question is raised. The result is that for practical purposes there is a compromise at present, which is not satisfactory but which seems the only practical way of dealing with the situation.

Dr. Zilboorg objects to the terms "legal insanity" and "medical insanity." If, however, one realizes that the term "medical insanity" means that a person is suffering from a mental disorder to such a degree that his commitment to a hospital for mental diseases is necessary, this term has a specific meaning. If one realizes that the term "legal insanity" means that a person is suffering from a mental disorder to such a degree that he is to be considered irresponsible for his acts, there is a definite meaning for this term. Whether the definition of "legal insanity" is proper or suitable is a different question.

DR. BERNARD GLUECK: There is distinct value in an occasional critical review of this topic, such as has been excellently made by Dr. Zilboorg. I thoroughly appreciate also what Dr. Bowman had to say. After all, issues have to be met as well as possible when they arise in daily practice. Theoretically, the solution to this perplexing, and commonly nasty, business of expert medical testimony seems to be simple. It consists in approximating the technic of this procedure as closely as possible to that of a medical consultation. All that is necessary is for the physicians on the opposing sides of an issue to come to an agreement concerning the facts in a given case, present the facts and leave the legal implications to the decision of the court. However, I have never succeeded in getting lawyers to agree to such a procedure. The Briggs law in Massachusetts approximates closely such a goal, although the procedure is different.

At any rate, no physician need feel compelled to go beyond his sphere of activity as a physician and permit himself to become involved in legal definitions. I know of no law which compels an expert to go beyond stating his findings in a given case.

I was much interested in what Dr. Overholser had to say about the McNaghten rule. Evidently, it permits the judge considerable leeway in determining the legal implications of a psychiatric diagnosis.

DR. GREGORY ZILBOORG: I cannot refrain from making at least one or two concluding remarks that are to me of utmost importance. First, if one recalls my statement that there is a tendency on the part of the medical profession to meet the law half way, one will realize that this is my redundant way of saying: Try to be practical. I believe there is only one way of being practical. If I am a clinician, I cannot express my opinion as to the sanity or insanity of a piece of carpenter work. I can speak only of the sanity or insanity of the carpenter who made it. As was pointed out by Dr. Jelliffe, legal insanity is a definition. So far as it is a definition, one cannot make any test of the rightness or wrongness of this. It is a fact. I limited my paper to capital crime because there social hatred comes into relation with the criminal, but one should remember that the best and most practical way out of this situation is, as was said by Weyer, to go one's own pace and first to claim with humility, which in this case is legitimate pride, what one knows, and that one does not know more. I doubt whether the courts would be able to withstand such an onslaught of passive scientific resistance. The fact that the courts consult the physician because he has the M.D. degree should make one realize they must believe the physician; one might say: "because I am a physician I do not know." I am afraid that those who try to compromise will find themselves in the same position as the compromise made by Thomas

Aquinas in the thirteenth century, when the church forbade any one to read Aristotle; Aquinas studied him and was fascinated by him, and he promulgated the great dogma, which is still followed, that Aristotle was right, but that the theological view was also right, because what is true in theology may not be true in philosophy and what is true in philosophy may not be true in theology. Verbal compromises on clinical facts will not help to the discovery of actual truth.

Dr. Jelliffe's reference to the Romans is of interest. One may recall that the man who established the word "insania" was an excellent fighter for psychiatry. It was Cicero. He made many speeches on the subject before the Roman senate, some of which are reminiscent of those made before this society when one asks the courts and society to give the psychiatrist a clinical chance!

Book Reviews

Die Epilepsie des Kindesalters. By Eugen Schreck. Pp. 173. Stuttgart, Germany: Ferdinand Enke, 1937.

The author's problem was to investigate the numerical relationship of the appearance of genuine and of symptomatic epilepsy. He concludes that it is no longer feasible to divide epilepsy into "genuine" and "symptomatic" forms, but that a third group must be differentiated: that of "symptomatic epilepsy in children tainted with hereditary diseases." This sounds reasonable, but most of the author's long discussion of "symptomatic epilepsy, on the one hand, and genuine epilepsy, on the other" seems meaningless to the reviewer.

Schreck discusses his own material and presents data on 44 cases of "symptomatic" epilepsy, 15 cases of "genuine" epilepsy and 43 cases that fall into his third group of "hereditary tainting." His division of cases into those of "symptomatic" and those of "genuine" epilepsy depends on the evidence for "early organic injury to the brain," and regularity and uniformity of fits in the former, as apposed to evidence for "hereditary taint" and irregularity of the convulsive phenomena in the latter.

Numerically, these forms appeared in his series of 330 cases as follows: (1) pure genuine epilepsy with proof of hereditary taint, 73 cases; (2) pure symptomatic epilepsy, exclusively acquired by organic injury to the brain, 168 cases, and (3) symptomatic epilepsy with at the same time proof of hereditary taint, 89 cases.

In discussion, Schreck says: "Genuine epilepsy has been regarded for a long time as depending on a hereditary inferiority. The conclusion arising from this as to the necessity of proof of a hereditary taint has been drawn, but the demand has not been completely fulfilled. I have not, therefore, been content with the designation of 'genuine,' 'essential,' 'idiopathic,' 'functional' and 'dynamic' epilepsy. . . . . As long as one does not commit oneself to the definite line of separation, namely, that for the exclusion of organic symptoms in genuine epilepsy a positive sign of the proof of hereditary taint is necessary, so long will the evaluation of epilepsy be unsatisfactory. If, for purely scientific reasons, one must place entire emphasis, in the postulation of genuine epilepsy, on the presence of a provable hereditary taint, from a practical point of view, the newly formulated law of heredity demands all the more a preceding event of this type."

It is apparent that Schreck regards "genuine" epilepsy as synonymous with "hereditary" epilepsy. The reviewer applauds any definition that will make more definite the meaningless term "genuine," but it is not easy to say in which cases there is an inherited factor and in which there is not. Schreck seems entirely to miss the important modern conception of epilepsy, i. e., that it is merely a symptom —repeated fits—and that fits, like most other symptoms, are caused by many different pathologic mechanisms. Thus, an inherited disease of the brain (such as Friedreich's ataxia) may cause hereditary fits, but such a condition certainly cannot be called "genuine" epilepsy. The same argument applies to the inherited cerebral aplasias, which account for so many cases of feeblemindedness with associated "epilepsy." Moreover, it is clear that if a disease is inherited it must have a structural basis.

Autogenes Training als Erlebnis: Protokoll einer psychologischen Entwicklung. By Dorothea Heugel. With foreword by J. H. Schultz. Price, 4.80 marks. Pp. 70. Zentralbl. f. Psychotherapie, 1938. Supp. 2.

This report is a record of observations in self training in relaxation, made daily for thirty-seven days and then weekly for sixteen weeks. The observer was a young woman described in the preface as belonging to an "artistically and mentally

superior clan." Presumably this is meant to imply that she is an Aryan. For years she had suffered from disturbances of sleep and from vascular and other vegetative upsets, without organic basis. Under medical direction she attempted in daily practice sessions to achieve relaxation by autosuggestion, meanwhile noting in minute detail her sensations and feelings. She concentrated, for example, on the idea of "quiet," whereon she noted a sensation of coolness in the temples, or after the self suggestion to relax a slight warmth occurred in the axillas. Again, in thinking of sun or heat she learned to ignore the resulting sensations of warmth. Finally, success was achieved in that she enjoyed deep, continuous sleep; her friends noted an absence of tension in her features, and when threatened with an attack of "heart weakness" she was able to regulate her breathing and achieve "an absence of all vascular disturbances," this acquired control of energies resulting in an enriched inner life.

The publication is illustrative of the introspective type of report popular in Titchener's time, but is scarcely a contribution to modern psychology. Its only value appears to be the implication that autonomic disturbances may be brought under control to some extent by a process of practiced self discipline. The style offers considerable difficulty because of attempts to obviate all foreign influences on the German language.

Tumors of the Nervous System. Proceedings of the Association for Research in Nervous and Mental Disease. Vol. XVI. Pp. 493, with 213 illustrations and 64 tables. Baltimore: Williams & Wilkins Company, 1937.

This publication consists of 16 chapters by 29 contributors to a symposium on tumors of the nervous system at the 1935 meeting of the Association for Research in Nervous and Mental Disease. Needless to say, it is comprehensive and covers numerous aspects of the problem, including such subjects as the metabolism of the tissues of the central nervous system, their antigenic properties and the condition of the cerebrospinal fluid in association with them. The book is a necessary adjunct to the library of any one interested in this subject.